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RESULTS OF THREE YEARS' EXPERIENCE WITH MICROBIOLOGICAL ASSAY OF VITAMIN B_{12} IN SERUM

BY

G. H. SPRAY, D.Phil., and L. J. WITTS, M.D., F.R.C.P.

Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

An improved method for the microbiological assay of vitamin B_{12} in serum using *Lactobacillus leichmannii* as test organism was developed in this department (Spray, 1955) and has been in regular use for the past three years. Although no new facts have been discovered, results have been obtained from patients with a variety of conditions. It is felt that a summary of these results may be of interest, illustrating the value of the method in diagnosis and confirming and extending observations already published.

Methods

Blood is collected in carefully cleaned all-glass syringes with stainless-steel needles, and is allowed to clot in acid-cleaned bottles. The clot is broken up with a glass rod, the blood is centrifuged, and the serum is removed and stored in a deep-freeze until required for assay. Details of the extraction process and the technique of the assays have been described elsewhere (Spray, 1955). In accordance with the accepted convention, results are expressed as micromicrogrammes ($\mu\mu$g. or 10^{-12} g.) of vitamin B_{12} activity per ml. of serum.

Results

The accompanying Chart illustrates the results obtained in the main groups of patients with macrocytic anaemia and related conditions.

Normal Subjects.—Results have been obtained from 123 normal subjects. The values ranged from 150 to 1,000 $\mu\mu$g. per ml., with a mean of 450 $\mu\mu$g. per ml.

Untreated Pernicious Anaemia.—Results have been obtained from 94 patients with pernicious anaemia in relapse. Of these, 85 gave values of 100 $\mu\mu$g. per ml. or less. In 7 the values were between 100 and 170 $\mu\mu$g. per ml., but only one of these (170 $\mu\mu$g. per ml.) was above the observed lower limit of the normal range. The mean of the results from these 92 patients is 64 $\mu\mu$g. per ml. The figures for the remaining two patients, who appeared to satisfy all the usual criteria for untreated pernicious anaemia, were 380 and 500 $\mu\mu$g. per ml. No explanation for these anomalous results was found, but contamination of the specimens from syringes or containers, or the possibility that the blood may have been taken after vitamin B_{12} had been given to the patients, cannot be excluded.

Diseases of the Central Nervous System.—In a few patients the first evidence of a deficiency of vitamin B_{12} is subacute combined degeneration of the spinal cord rather than anaemia. Determination of vitamin B_{12} in the serum is a simple way to see whether a patient believed to be suffering from subacute combined degeneration is deficient in vitamin B_{12}, or whether some other cause should be sought for the symptoms. The estimation has been carried out on sera from 27 patients in whom a diagnosis of subacute combined degeneration was suspected. In eight of these patients the clinical and laboratory findings were suggestive of vitamin-B_{12} deficiency, but there was usually some feature, such as a relatively normal blood picture or a normoblastic bone marrow, which raised doubts about the diagnosis. All these patients showed abnormally low levels, seven being below 100 $\mu\mu$g. per ml. and the other being 110 $\mu\mu$g. per ml. Thus these results confirmed the clinical diagnosis, and seven of the patients showed improvement after treatment with vitamin B_{12}. In four patients the response was very good, and it was good in another two. One patient showed only slight improvement, and one had not improved up to six months after starting treatment. Despite this lack of response the neurologist who was asked to assess the case felt that the evidence for deficiency of vitamin B_{12} was quite good.

The remaining 19 patients in whom deficiency of vitamin B_{12} was thought possible on clinical grounds included four on whom the final diagnosis was cervical spondylosis, three with disseminated sclerosis, three with unexplained paraesthesiae, and six with miscellaneous diagnoses such as pre-senile dementia, unexplained peripheral neuropathy, arteriosclerotic parkinsonism, and dizziness. All of these patients had normal concentrations of vitamin B_{12} in the serum, ranging from 160 to 780 $\mu\mu$g. per ml. Only two of the results (160 and 170 $\mu\mu$g. per ml.) were so low as to suggest the possibility of deficiency of vitamin B_{12}, but both of these figures were much higher than the highest figure found in patients with proved subacute combined degeneration. In most instances vitamin B_{12} was not given to the patients, but in those patients in whom it was tried there was little or no suggestion of a response.

Pernicious Anaemia of Pregnancy and the Puerperium.—Sera from 22 patients with this condition have been examined. The results ranged from 60 to 600 $\mu\mu$g. per ml., with a mean of 237 $\mu\mu$g. per ml. Only four of the values were below the normal range, but the mean for this group of patients is significantly lower than the normal mean ($n=143$, $t=5.65$, $p<<0.001$).

Partial Gastrectomy.—Badenoch, Evans, Richards, and Witts (1955) showed that megaloblastic anaemia can occur after partial gastrectomy, and that the patients may be unable to absorb vitamin B_{12} from the gut. It was therefore

of interest to measure vitamin B_{12} in the serum of patients who developed macrocytic anaemia after partial gastrectomy. Serum has been obtained from 14 such patients. The bone marrow was examined in most of these patients and showed megaloblastic degeneration. The results ranged from 18 to 480 $\mu\mu$g. per ml., with a mean of 164 $\mu\mu$g. per ml. Repeat observations were obtained on four of these patients at times between two weeks and six months after the date of the first serum. The later figures were all in accord with the first, in one instance confirming a deficiency of vitamin B_{12}, and in another suggesting an aggravation of the deficiency. The supplementary figures are not included in the quoted range or mean. Of the 19 observations on these 14 patients, 11 are below the normal range and 3 more are towards the lower limit of normal.

These results confirm the earlier observations (Badenoch *et al.*, 1955; Mollin and Ross, 1957) that deficiency of vitamin B_{12} may develop some years after partial gastrectomy. Nevertheless the mean value is higher than that in pernicious anaemia, and this would suggest that lack of vitamin B_{12} is not the only factor in the development of megaloblastic anaemia after partial gastrectomy. In an attempt to obtain further information on the frequency of this sequel to the operation, the level of vitamin B_{12} was estimated in the serum of 21 randomly selected patients who had had a partial gastrectomy five years or more previously. The results ranged from 99 to 750 $\mu\mu$g. per ml., with a mean of 270 $\mu\mu$g. per ml. Two of the patients gave results below the observed lower limit of the normal range, and the mean of all these values was significantly lower than the normal mean ($n=142$, $t=4.53$, $p<0.001$). However, the mean was significantly higher than the mean for the 14 patients who showed signs of faulty blood formation ($n=33$, $t=9.31$, $p<<0.001$).

Total Gastrectomy.—It has been possible to study only one patient with megaloblastic anaemia following total gastrectomy. He gave the very low value of 17 $\mu\mu$g. per ml. as the mean of the results of three separate assays.

Diverticulosis of Small Intestine and Blind Loop Syndrome.—Because of the occurrence of megaloblastic anaemia in some patients with diverticulosis of the small intestine (Badenoch, Bedford, and Evans, 1955), or with blind loops left after surgery (Cameron, Watson, and Witts, 1949), estimations of vitamin B_{12} have been made on the serum of three patients with diverticulosis and two with a blind loop. One patient with diverticulosis had a megaloblastic marrow, but the marrow was not examined in the other two cases; both patients with blind loops had megaloblastic marrows. All five of these patients had abnormally low levels of vitamin B_{12} in the serum.

Malabsorption Syndrome.—Some patients with steatorrhoea develop megaloblastic anaemia, so that it was of interest to determine the concentration of vitamin B_{12} in the serum of such patients. Serum was obtained from 11 patients in whom malabsorption was confirmed by fat balance or similar tests, and who showed changes in the bone marrow or peripheral blood suggestive of deficiencies of vitamin B_{12} or folic acid. The results ranged from 10 to 320 $\mu\mu$g. per ml., with a mean of 176 $\mu\mu$g. per ml. Four of the results were below the normal range, and two more were only just above the lower limit of normal, so that in a considerable proportion of these patients there was probably a deficiency of vitamin B_{12}.

Nutritional Megaloblastic Anaemia.—Estimations have been made on sera from two patients with megaloblastic anaemia due to dietary deficiencies. The first patient, who had taken a strict vegetarian ("vegan") diet for 20 years, had a level of 46 $\mu\mu$g. per ml. The second patient, whose diet had been deficient in meat and meat products, milk, and fish for at least six years, gave the slightly subnormal level of 120 $\mu\mu$g. per ml.

Megaloblastic Anaemia Due to Anticonvulsants.—Only two patients with this condition have been available for study. One gave the normal result of 260 $\mu\mu$g. per ml., and in the other the abnormally low level of 73 $\mu\mu$g. per ml. was obtained.

Leukaemia, Polycythaemia, and Related Conditions.—The results obtained in leukaemia, polycythaemia, and related conditions are summarized in the Table. No children were studied, which explains the absence of cases of acute lymphatic leukaemia. The serum was examined before any treatment was given. All the patients with chronic myeloid leukaemia gave abnormally high results, while patients with chronic lymphatic leukaemia gave normal values. In

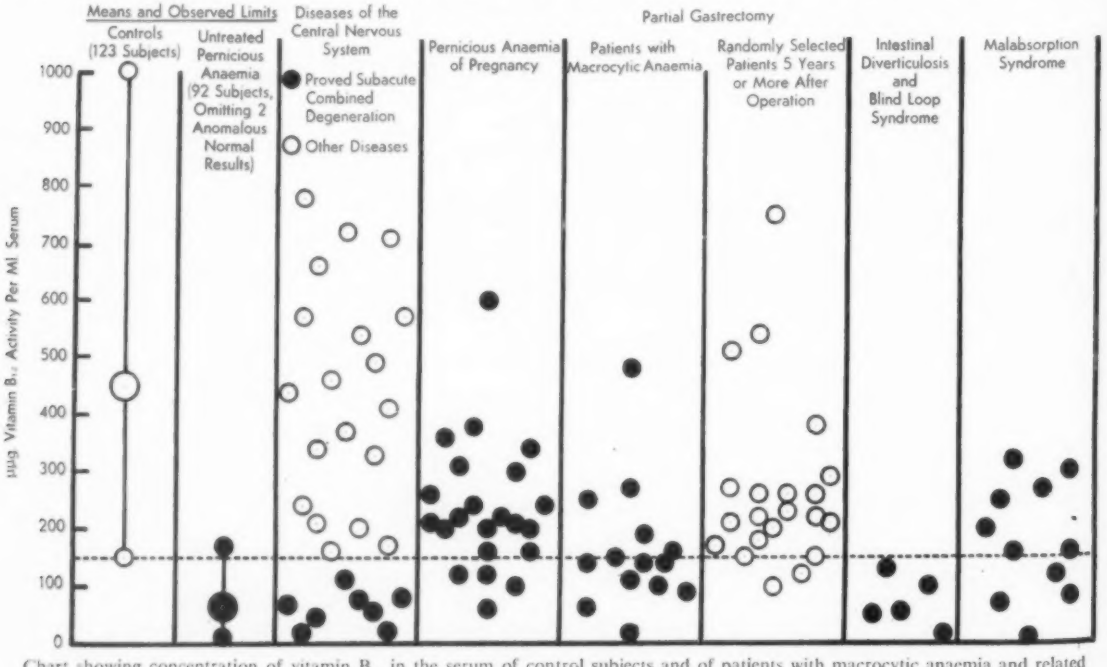

Chart showing concentration of vitamin B_{12} in the serum of control subjects and of patients with macrocytic anaemia and related conditions. The broken line shows the lower limit of normal range.

monocytic leukaemia, the acute leukaemias, and polycythaemia vera both normal and high values were obtained, but the highest figures found in polycythaemia were much lower than in the leukaemias. One patient with polycythaemia showed an abnormally low level, for which no explanation was found. Of two patients with erythroleukaemia, one gave a normal value and in the other the level was slightly raised. The only patient with myelosclerosis gave a slightly raised result, while two patients with multiple myeloma both showed levels a little below the lower limit of the normal range. In general these findings are in agreement with published results (Beard *et al.*, 1954; Erdmann-Oehlecker and Heinrich, 1956; Mollin and Ross, 1955).

Concentration of Vitamin B_{12} in Serum of Patients with Leukaemia, Polycythaemia, and Related Conditions

Condition	No. of Cases	$\mu\mu$g.* Vitamin B_{12} Activity per ml. Serum		No. of Patients Showing Abnormally High Values
		Range	Mean	
Chronic myeloid leukaemia ..	5	1,600–6,400	4,580	5
,, lymphatic leukaemia ..	2	460– 510	485	Nil
Monocytic leukaemia	9	300–3,000	1,050	4
Acute myeloblastic leukaemia ..	5	400–5,800	1,800	2
,, undifferentiated leukaemia	3	540–6,600	3,880	2
Polycythaemia vera	10	100–2,200	831	2
Erythroleukaemia	2	510–1,800	1,160	1
Myelosclerosis	1	1,300	—	1
Multiple myeloma	2	110– 120	115	Nil

Haemochromatosis.—Assays have been carried out on serum from two patients with haemochromatosis. The results were 1,400 and 1,800 $\mu\mu$g. per ml. The reason for these abnormally high results in this condition is not clear. Perhaps the excessive deposits of haemosiderin in the liver and elsewhere immobilize the sites where vitamin B_{12} is normally stored, so that the vitamin cannot be taken up in the usual way. This could result in the presence of abnormally large amounts of the vitamin in the serum. Abnormally high levels have been found in patients with cirrhosis of the liver (Rachmilewitz *et al.*, 1956), and it was suggested that in these patients stored vitamin B_{12} might be released from damaged liver cells.

Discussion

With a method of the sort used in this investigation it is impossible to make a strict comparison of the results with those of other workers, because different methods yield rather widely different figures in different types of subject. Hence abnormal figures can be compared only with the normal range established by the same method, and comparison with the results of other methods must be limited to general trends.

The results make it possible to draw certain inferences about the usefulness of serum vitamin B_{12} estimations, both in diagnosis and for making decisions about treatment. The value of the test in untreated pernicious anaemia is well established, and the present results provide further evidence that, although occasional anomalous results are obtained, the test gives clear evidence of vitamin B_{12} deficiency in the vast majority of patients with this condition. In neurological disorders this comparatively simple test makes it possible in most instances to distinguish clearly between patients whose disease is due to deficiency of vitamin B_{12} and those in whom there is some other cause for the symptoms.

The test shows that the megaloblastic anaemias which occasionally develop after partial gastrectomy, or in patients with massive diverticulosis of the small intestine or with blind loops left after surgery, are usually associated with deficiency of vitamin B_{12}, though this may not be the only deficiency present. It is also apparent that in patients who have had a partial gastrectomy for five years or more the level of vitamin B_{12} in the serum tends to be lower than in health.

The results obtained in pernicious anaemia of pregnancy and the puerperium indicate that these patients often have a mild degree of vitamin B_{12} deficiency, which may explain why they respond to large doses of vitamin B_{12} (Moore *et al.*, 1955), but depression below the lower limit of the normal range is infrequent. Heinrich (1954) has shown that the level of vitamin B_{12} in the serum is low in 20% of pregnant women who are otherwise normal, so that there is probably no difference in the vitamin B_{12} status of pregnant women with megaloblastic anaemia and those with uncomplicated pregnancy.

Low levels of vitamin B_{12} were found in the serum of a considerable proportion of patients with the malabsorption syndrome, where folic acid is the treatment of choice. In such patients the test may be of value because some patients need vitamin B_{12} before they respond to folic acid (Nieweg *et al.*, 1952), and the finding of a low serum vitamin B_{12} would indicate that vitamin B_{12} as well as folic acid should be given. For instance, one of the patients included in this group had a serum vitamin B_{12} of 70 $\mu\mu$g. per ml., and was thought to have pernicious anaemia. He failed to show any response to vitamin B_{12}, but had a typical response as soon as folic acid was given. Fat-balance studies later showed that he had steatorrhoea.

The low results in the two patients with nutritional megaloblastic anaemia provide further evidence that patients may become depleted of vitamin B_{12} after taking a diet which is deficient in animal products for a long period. The result in one of the two patients with megaloblastic anaemia after anticonvulsant therapy indicates that this type of anaemia may sometimes be associated with deficiency of vitamin B_{12}. This is in keeping with the observation that a few of these patients respond to vitamin B_{12}, although the majority appear to require folic acid.

In leukaemia and allied conditions abnormally high levels of vitamin B_{12}, rather than low ones, are often found, and this observation may provide the basis for a useful aid to diagnosis. High figures seem to be typical of chronic myeloid leukaemia, whilst normal values are found in chronic lymphatic leukaemia. In other types of leukaemia and in polycythaemia vera the result may be either normal or high, but the test may still be of value. For instance, in a patient suspected to be suffering from polycythaemia vera a high result would confirm the diagnosis, but a normal one, although not excluding this diagnosis, would suggest the possibility that there may be another cause for the clinical findings.

Summary

The results obtained with the microbiological assay of vitamin B_{12} in the serum of various types of subject are presented.

The range of values found in 123 normal subjects was from 150 to 1,000 $\mu\mu$g. per ml., with a mean of 450 $\mu\mu$g. per ml. Of 94 patients with pernicious anaemia in relapse, 85 gave values of 100 $\mu\mu$g. per ml. or less, seven gave values between 100 and 170 $\mu\mu$g. per ml., and two anomalous normal results were obtained.

In subacute combined degeneration of the spinal cord the vitamin B_{12} in the serum is reduced to the same levels as in pernicious anaemia, and this has proved useful in differentiating the condition from other diseases of the nervous system.

There is a moderate reduction in the vitamin B_{12} in the serum in pernicious anaemia of pregnancy, but not usually to the same degree as in Addisonian pernicious anaemia.

A considerable proportion of patients who develop megaloblastic anaemia in association with partial or total gastrectomy, diverticulosis of the small intestine, blind loops left after surgery, the malabsorption syndrome, dietary deficiency and anticonvulsant therapy are shown to be deficient in vitamin B_{12}.

Abnormally high results were obtained in all the patients with chronic myeloid leukaemia, but in chronic

lymphatic leukaemia the results were normal. In the acute leukaemias and in polycythaemia vera both normal and high results were found.

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PORPHYRIA

A SOUTH AFRICAN SCREENING EXPERIMENT

BY

GEOFFREY DEAN, M.D., M.R.C.P.
Senior Physician, Provincial Hospital, Port Elizabeth, South Africa

AND

H. D. BARNES, Ph.D.
South African Institute for Medical Research, Johannesburg

Garrod (1923) credits Gunther with the first recognition that porphyria was an "inborn error of metabolism." If the term "porphyria" is confined to inborn errors of porphyrin metabolism, it excludes purely acquired disturbances whether of a temporary or permanent nature. An increase of porphyrin production and excretion without a genetic basis could be termed "hyperporphyrinism."

It is essential to distinguish between the genetic and purely acquired disturbances of porphyrin metabolism, because an attack of "acute porphyria" with the possible death of the patient occurs only if the gene for porphyria has been inherited. Diagnosis of porphyria in the latent phase is most valuable because in this disorder acute attacks are usually precipitated by the inadvertent use of certain commonly prescribed drugs, particularly barbiturates.

The classification of the porphyrias has in the past presented many difficulties, and the classification was symptomatic. In 1937 Jan Waldenström made a brilliant clinical survey of 103 cases of acute porphyria in Sweden; among these cases light sensitivity did not occur. He also reviewed the published cases where light sensitivity had only occurred in adult life, and these cases he termed "porphyria cutanea tarda." A third very rare type of porphyria has been described. In this type light sensitivity is present from birth, the urine is dark red because of the high excretion of porphyrin, and anaemia and splenomegaly are present. This very uncommon type of porphyria has been called "congenital porphyria" (Gunther, 1922). Schmid, Schwartz, and Watson (1954) classified the porphyrias on the basis of the porphyrin content of the liver and bone marrow of 31 cases. In two cases of congenital porphyria they found porphyrins concentrated in the bone marrow, and this rare group they named "porphyria erythropoietica." In the remaining 29 cases porphyrins were mainly found in the liver and they were therefore classified as porphyria hepatica. This group included the type described by Waldenström, a mixed type in which photosensitivity and acute symptoms may occur in the same patient, and possibly a third group of purely cutaneous type unassociated with acute attacks.

Genetic Classification

A plea is now made that the term "porphyria" should be reserved for the genetic disease only, for inborn errors of porphyrin metabolism, and that the porphyrias should be classified according to their genetic basis, as this would appear to be a fundamental method of classification.

There are three clearly defined genetic types of porphyria; there may be more.

1. *The Congenital Type, or Porphyria Erythropoietica.*—This is exceedingly rare and should be easily diagnosed by the marked light sensitivity from birth, the dark-coloured urine, anaemia, splenomegaly, and pink staining of the teeth. It is thought to be inherited as a Mendelian recessive characteristic (Cockayne, 1933).

2. *The Swedish Type of Porphyria Hepatica.*—This is the type described by Jan Waldenström, who has now collected over 320 patients with this disorder (Waldenström, 1957). He has shown that it is inherited as a Mendelian dominant characteristic and many of his families trace back to an original forebear from Northern Sweden. This type corresponds to the acute intermittent group of the classification of Schmid *et al.* Most cases of acute porphyria in Europe and in the United States belong to this group.

It has the following characteristics: (1) It is inherited as a Mendelian dominant gene and is not sex-linked. (2) Acute attacks occur most commonly in females between the ages of 16 and 50. (3) Acute attacks are often precipitated by drugs, especially barbiturates. (4) Light sensitivity does not occur. (5) There is a high excretion of porphobilinogen G. and amino-laevulinic acid in the urine during the acute attack and for a long time afterwards. If the disorder is causing symptoms, the Erhlich reaction (Schmid *et al.*) is usually positive. (6) There is either no increase or very little increase in urinary and faecal porphyrin excretion except during an acute attack. (7) In a porphyric family it is difficult to detect all the latent cases. However, the majority of latent cases can be suspected if not proved by using quantitative methods of analysis for porphobilinogen and amino-laevulinic acid. If there has been an acute attack in the previous few years the increase in porphobilinogen is usually sufficient to give a positive Ehrlich reaction.

3. *The South African Type.*—A number of papers (Barnes, 1945, 1951; Murray, 1949; Barnes and Marshall, 1952; Dean, 1953, 1956, 1957; Dean and Barnes, 1955) have shown that porphyria is a common disorder among the European population of South Africa. It is genetically different from the Swedish, or Waldenström, type, and has the following characteristics: (1) It is inherited as a Mendelian dominant gene and is not sex-linked (Barnes, 1945). (2) Acute attacks occur most commonly in females between the ages of 16 and 50. (3) Acute attacks are in our experience always precipitated by drugs, especially barbiturates. The acute attack resembles the acute attack in the Swedish type and in the past was usually fatal. (4) Light sensitivity will usually be found in some of the affected male members of the family, but it may be very slight or absent in the females. (5) There is a high excretion of porpho-

bilinogen during the acute attack, but the excretion returns to normal as the patient recovers. (6) There is greatly increased excretion of urinary and faecal porphyrin during the acute attack. (7) Latent porphyria can be detected by the slight increase in urinary and definite increase in faecal porphyrin excretion. For routine testing the detection of increased faecal porphyrin is particularly valuable. The Ehrlich reaction, however, in the quiescent phase is practically always negative.

In this type acute attacks, cutaneous manifestations, and symptomless cases with only increased excretion of porphyrin occur in the same family group, and are different manifestations of the same inherited disorder, just as asthma, hayfever, and eczema are different manifestations of inherited atopy.

Incidence in European South Africans

Porphyria is common among European South Africans because a very small group of early settlers have multiplied in ideal surroundings, so that to-day 1,000,000 of the present 3,000,000 white population hold the names of 40 original settlers and are direct descendants of those settlers in the 9th, 10th, 11th, and 12th generations. One of these early settlers was a porphyric. A subsequent paper will demonstrate that practically all South African porphyrics of European stock are descendants of this original prolific forebear who married at the Cape in 1688. That porphyria is a common disorder in South Africa is attested by the fact that one of us (G. D.) has diagnosed 564 cases of porphyria in 54 family groups.

Screening for Porphyria

In the Swedish type of porphyria the Ehrlich aldehyde test will usually be positive if the disorder is causing symptoms. To screen a large group taken at random for this type of porphyria in order to estimate the incidence of the disease will present great difficulty until a simple method for detecting slight increase in porphobilinogen and amino-laevulinic acid has been discovered, but once a case of porphyria has been diagnosed, all other members of the family should be investigated.

In the South Africa type the Ehrlich reaction is positive only during the acute phase. The disease is very common in South Africa, and the problem has been how to diagnose the disorder while the patient is still well and before an acute attack is precipitated by the inadvertent use of barbiturate drugs or a thiopentone anaesthetic. Fortunately the faecal and often the urine porphyrin excretion is usually above normal in adult porphyrics. The increased urinary porphyrin can be detected spectroscopically, although this is sometimes difficult, and by extraction with a solvent which then shows purple fluorescence in ultra-violet light.

The most useful test in the consulting-room can be carried out with a small fragment of stool; a little obtained on the end of a gloved finger by a "rectal examination" is sufficient. The small specimen is dissolved in 2 ml. of a solvent consisting of equal parts of glacial acetic acid, amyl alcohol, and ether. The brown, supernatant fluid is then decanted and viewed by ultra-violet light, using Wood's filter. In this light the negative specimens show a green or grey fluorescence. If there is an excess of porphyrin the fluorescence is a brilliant pink. A few specimens fall into an intermediate "doubtful" group, and an excess of chlorophyll can also cause pink fluorescence. In the positive and doubtful cases a quantitative analysis of faecal coproporphyrin and protoporphyrin is then carried out, and the urine is also examined for porphyrin excess.

The detection of increased porphyrin excretion is not a diagnosis of porphyria; the increased excretion may simply be due to a temporary hyperporphyrinism, often because of liver dysfunction, but sometimes of unknown aetiology. The possibility of porphyria must then be considered.

The diagnosis of porphyria of South African type in the non-acute state is sometimes difficult and time-consuming. The following factors should be taken into consideration: (1) The personal history; particularly any history suggestive of a previous attack of acute porphyria. (2) Whether the skin, particularly on the back of the hands, abrades and blisters easily, or has done so in the past. The skin on the back of the hand should be scraped with the finger-nail to see if it abrades easily. (3) Increased porphyrin excretion in the urine and faeces, particularly if this persists for some months. Normal total faecal porphyrin does not usually exceed 70 μg./g. dry weight. (4) The finding of other affected members of the family is important evidence in favour of porphyria. A careful family history should be taken and a family tree of all the relations should be drawn. These relations should then be interviewed and specimens obtained from them for porphyrin analysis. Often a number of them will be more clearly porphyrics than the patient who is first seen.

Results of Screening in South Africa

Two groups of the community were screened for porphyrin in order to help establish the incidence of the disorder in South Africans of European stock. The first group consisted of 608 patients from a mental hospital. The second group consisted of 645 nurses from four hospitals who voluntarily took part in the experiment.

Among the 608 mental hospital patients the sexes were about equal; the specimens were examined in small batches because it is not wise to screen too many specimens in a day as the ultra-violet light has an irritating effect on the eyes. Seven patients had greatly increased porphyrin excretion, in four of whom (Cases 1–4) this was considered due to porphyria (see Table I and case histories below).

Case 1.—No history of acute attack but skin abraded easily. High faecal and urinary porphyrin on four occasions. Member of family group (already investigated by G. D.) with 36 known porphyrics, of whom at least three have died from acute porphyria in the last few years.

Case 2.—No history of acute attack but skin abraded easily since age of 18. Persistently raised faecal and urinary porphyrin. Another member of family affected.

Case 3.—Recurrent blisters and sores on hands for past 15 years. Skin abraded with the slightest scratch. General health

TABLE I.—*Porphyria Among Patients at Mental Hospital*

Case No.	Sex and Age	Faecal Porphyrin (μg. g.)			Porphyrin in Urine	Mental Disorder	Skin Sensitivity *	Porphyrics in Family Study	Acute Attacks
		Copro-	Proto-	Total					
1	F 37	46	115	161	++	Epilepsy. Congenital blindness	+	36	Minor attacks
2	F 43	31	113	144	+	Catatonic schizophrenia	+	1	None known
3	M 33	327	259	586	+	,, ,,	++	—	,, ,,
4	F 36	210	740	950	+	Depressive psychosis after acute porphyria	++	27	Acute porphyria six months before admission
					Hyperporphyrinism Not Due to Porphyria				
5	F 83	596	445	1,041	+	Dementia	+	—	None known
Six months later					—	Mentally improved	—	—	
6	M 58	31	90	121	—	Congenital imbecile	—	—	None known
7	F 66	12	66	78	—	Congenital syphilitic imbecile	—	—	,, ,,

* Skin sensitivity. + = No scars or sores on skin, but skin on back of hand can be abraded with finger-nail more easily than usual. Skin sensitivity slight. ++ = Skin can be easily abraded and sores or scars are present. +++ = Skin sensitivity is marked with blisters and sores.

and nutrition good; not on drugs. Faecal and urinary porphyrin high on four occasions. No member of family traced.

Case 4.—Attended by G. D. in 1956 during severe acute attack. Developed a depressive psychosis a few months after recovery, but responded excellently to E.C.T. At least one relation died from acute porphyria.

In the remaining three patients the raised porphyrin excretion is thought to have been caused by temporary hyperporphyrinism.

Case 5.—Very high faecal and urinary porphyrin and skin abraded easily shortly after admission, when extremely malnourished and mildly demented. With good feeding porphyrin levels slowly fell, general condition improved, and skin no longer abraded. No personal or family history of increased skin sensitivity or increased porphyrin excretion; members of family examined normal. The hyperporphyrinism was probably due to a disturbance of liver function.

Case 6.—Faecal porphyrin raised only when first tested. Skin not sensitive, urine normal, no family history.

Case 7.—Faecal porphyrin at first just above normal, later normal. Skin not sensitive.

Specimens for examination were received from 645 nurses. Of these, 28 stools gave a pink fluorescence when examined by the method described and were sent for quantitative porphyrin analysis. In nine of these cases the fluorescence had been due to chlorophyll, but 19 nurses had a porphyrin excretion above 40 μg./g., four of these had an excretion level less than 70 μg./g., no history of a sensitive skin, and none of their relations were affected. The 15 remaining nurses were interviewed and their families were investigated, and 11 of them (Cases 8–18) were thought to have inherited the gene for porphyria (see Table II and case histories below).

TABLE II.—*Porphyria Diagnosed in Nurses*

Case No.	Sex and Age	Faecal Porphyrin (μg. g.)			Porphyrin in Urine	Skin Sensitivity *	Porphyrics in Family Study	Acute Attacks
		Copro	Proto	Total				
8	F 26	25	115	140	+	+	1	Minor attacks
9	F 46	105	470	575	+	−	4	Yes
10	F 28	38	134	172	− +	+ + +	1	Cutaneous porphyria
11	F 19	69	127	191	+	+	1	No
12	F 18	71	132	203	−	−	27	,,
13	F 21	98	107	205	+	+ +	37	,,
14	F 47	229	585	814	−	+ +	2	Yes
15	M 27	88	135	223	+ +	+	4	No
16	F 51	21	69	90	−	−	2	,,
17	M 52	12	51	63	−	+	2	,,
	Mother	33	105	138	−	+ +		,,
18	F 19	163	250	413	−	−	2	,,
	Father	51	52	103	−	−		,,
	Possible Further Cases Among Nurses							
19	F 18	10	52	62	−	−	3	
	Sister	46	94	140	+	+	−	
	Mother	19	57	76	+	+	−	
	Aunt	23	79	102	+	+	−	
	Hyperporphyrinism Not Due to Porphyria							
20	F 29	54	194	248	−	−	−	
21	F 31	172	142	314	−	−	−	
22	F 33	12	63	75	−	−	−	

* See footnote to Table I.

Case 8.—Long history of recurrent abdominal pain; apparently neurotic temperament. Skin abraded easily; excess porphyrin in faeces and urine on three occasions. Another member of family had sensitive skin and high porphyrin excretion.

Case 9.—Long thought neurotic because of unexplained complaints of abdominal pain and vomiting. Skin did not abrade easily, but high faecal and urinary porphyrin excretion. During acute attack had porphobilinogen in urine. Other members of family affected. At time of investigation laparotomy under consideration.

Case 10.—Received treatment for recurrent blisters on hands diagnosed as epidermolysis bullosa. Increased faecal and urinary porphyrin excretion. Another member of her family similarly affected.

Case 11.—Mildly sensitive skin that abraded easily; faecal and urinary porphyrin was raised on four occasions. Had been adopted as baby. Another member of family affected.

Case 12.—No skin sensitivity, but faecal and urinary porphyrin was repeatedly raised. Member of large family group of porphyrics.

Case 13.—Scars on hands from previous blisters; skin abraded very easily; raised faecal and urinary porphyrin. Member of family group of 37 known porphyrics.

Case 14.—In 1949 desperately ill after course of sulphonamides (severe abdominal pain, repeated vomiting, and red urine; mentally disturbed and partially paralysed). Skin abraded easily; faecal and urinary porphyrin raised on four occasions. Another member of family with high porphyrin excretion.

Case 15.—Patient and his father and uncle had very sensitive skins and high faecal and urinary porphyrin excretion.

Case 16.—Skin abraded easily; two members of family similarly affected; faecal and urinary porphyrin repeatedly raised.

Case 17.—Slight tendency for skin on hands to abrade; faecal porphyrin at upper level of normal, urinary porphyrin increased. Mother and brother more obviously affected.

Case 18.—Faecal porphyrin persistently very high; father's and paternal grandmother's faecal and urinary porphyrin greatly increased. Probably inherited genetic porphyria with absence of symptoms.

Case 19.—Diagnosis still in doubt. Porphyrin excretion at upper limit of normal, but sister, mother, and aunt had increased skin sensitivity and raised porphyrin excretion.

A further three nurses (Cases 20–22) had increased faecal porphyrin but later specimens were normal; they did not have a sensitive skin and no other affected members of their family could be found. They are thought to have had a temporary hyperporphyrinism.

Case 20.—Faecal porphyrin raised on two occasions only. Three members of family investigated with negative results.

Case 21.—Two months after first investigation porphyrin excretion was normal.

Case 22.—Porphyrin excretion persistently at the high side of normal.

Conclusions

Fifteen porphyrics were found among the total number (1,253) who were screened in this survey, an incidence of about 1%; this is a high incidence. Screening for porphyria should be routine practice in South Africa, and is, in our opinion, as important a routine test there as testing the urine for sugar.

It must be remembered that porphyria is much less common in other parts of the world, although not so rare as was formerly believed. Several hundred cases have been reported by Waldenström (1957) in Sweden and the disorder is not very uncommon in the United States.

When porphyria is diagnosed the danger of taking certain drugs should be explained. A letter should be given to the patient stating the evidence for the diagnosis and warning about the uses of drugs in this condition; this letter should be shown to any doctor subsequently consulted.

In the present survey 15 were thought to have inherited the gene for porphyria among 1,253 who were screened for the disorder. This suggests that the gene among the white population in the Eastern Cape Province of South Africa is about 1%.

Summary

Porphyria has been defined as an "inborn error of metabolism." This excellent definition distinguishes porphyria from hyperporphyrinism due to disturbances of porphyrin metabolism which are not of genetic origin.

Increased porphyrin excretion may be due to porphyria or hyperporphyrinism. It is important to distinguish between the two because in porphyria certain commonly used drugs may precipitate an acute disturbance of porphyrin metabolism with possible paralysis and death. Acute porphyria occurs only if porphyria has been inherited. Although the Swedish and South African types are genetically different disorders the acute attacks are very similar in both types.

The classification and diagnosis of porphyria are discussed. The methods used for detecting the South

African type of porphyria during the non-acute or quiescent stage are described.

The way to distinguish between porphyria and hyperporphyrinism is described; particular emphasis is laid on the importance of studying the relations of the patient. The differential diagnosis is sometimes difficult.

A simple method for screening the stool for excess porphyrin is described. Sufficient stool for the test can usually be obtained on the gloved finger while making a rectal examination. The urine should also be examined for porphobilinogen and excess porphyrin.

Two groups of South Africans were screened for porphyria using the methods described. Among the 608 patients at a mental hospital four were found to have porphyria, and among 645 nurses 11 were thought to have inherited this gene. The incidence among the nurses was greater than at the mental hospital, but the numbers are not sufficient to be statistically significant.

Screening for porphyria should be routine practice in South Africa, where the disorder is often found.

We would like to thank Professor Jan Waldenström, of Lund University, for enabling one of us (G. D.) to see a number of Swedish porphyric family groups. Professor Waldenström is in agreement with us that the Swedish type of porphyria is a different genetic disorder from the South African type. A detailed comparative study of these two types of porphyria is in progress.

We would like to thank Dr. Wolpowitz, the matron, and staff of Fort England Hospital, Grahamstown; Dr. McLean, the matron, and staff of Provincial Hospital, Port Elizabeth; Dr. Visser, the matron, and staff, of Provincial Hospital, Uitanhage; and Miss Roux, principal of the Sharley Cribb Training College, who all co-operated in the collection of the specimens. We also thank Professor W. H. Craib for his advice and constructive criticism.

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Nursing and Midwifery, the latest booklet in the Central Youth Employment Executive's "Choice of Careers" series, is the first of two companion booklets on nursing; the other, *Nursing for Men*, will be published later this year. After describing the rise of nursing as a profession, the booklet proceeds to deal with the different branches of nursing, such as hospital work, home nursing, work in clinics, health visiting, and industrial health nursing. The surroundings in which the work is done are illustrated by photographs. Training for nursing cannot begin until the age of 18, so advice is given for those who leave school earlier on "bridging the gap"—for instance, by attending pre-nursing courses and "cadet" schemes. There is a section on the personal qualities of the nurse: "She must have kindness, patience, and sympathy, yet she must not be sentimental or emotional, and must know when to be firm . . . there is no place in the nursing profession for the girl who scamps her work and trusts to luck." Other sections contain information about the training of nurses and midwives and about the many additional qualifications they may obtain. Finally the openings and prospects for nurses in Britain and overseas are touched upon. (Her Majesty's Stationery Office, price 1s. 9d. net.)

THE HUMAN SPERMATOZOON

BY

LORD ROTHSCHILD, F.R.S.

From the Department of Zoology, University of Cambridge

[WITH SPECIAL PLATE]

Until the advent of the electron microscope comparatively little was known about the fine structure of human spermatozoa. Even when this instrument and the thin-section technique became available, progress was slow because of the unusual fragility of human spermatozoa as compared, for example, with those of the bull or the ram. An important review, including a comprehensive bibliography, of the ultrastructure of the human spermatozoon was published in Sweden by Ånberg in 1957. As this is not readily available in the United Kingdom, the electronmicrographs reproduced on the Special Plate may be of interest.

Structure of Spermatozoon

A longitudinal section of the head and middle-piece of a spermatozoon is reproduced in Fig. 1, the probable plane of section being shown in the inset diagram. The head is bounded by the cell membrane, the acrosome terminating near the equatorial segment, and the nuclear membrane. The fragility of the human spermatozoon may be put to good purpose in identifying these structures, as they often become detached while the material is being prepared for electron microscopy, as in Fig. 2. Two vacuoles containing partially opaque material are present in the head. According to Ånberg there is a basal plate at the posterior end of the sperm head, but this is not visible in the specimen illustrated. The neck contains a remarkable structure which seems to consist of a series of electron-dense rings, somewhat reminiscent of vertebrae. They may be connected with the tail and middle-piece fibrils which are shown in the transverse section through the middle-piece in Fig. 3. The middle-piece consists of 29 fibrils embedded in a protoplasmic matrix and arranged as follows: an outer ring containing nine fibrils; an inner ring, concentric with the outer one, containing nine pairs of fibrils; and two fibrils located at the centre of the system. At first sight the inner ring may seem to consist only of nine fibrils; but close examination shows that each of the nine "fibrils" is, at the least, double.

One or, possibly, two mitochondrial sheaths or ribbons, bounded by the cell membrane, appear to be wound in a rather irregular spiral round the fibril system. According to Ånberg the mitochondria, whose characteristic structure is clearly visible in Fig. 3, do not form a spiral ribbon round the middle-piece; but Fig. 1 suggests that they do, even though the spiral is somewhat irregular. The plane of the section in Fig. 1 is such that the spherical head centriole described by Ånberg (1957) and by Burgos and Fawcett (1955) is not visible; nor is the tail, which would be over 100 cm. long at the magnification of Fig. 1. The tail contains 20 fibrils, the outer ring of nine, which can be seen in middle-piece sections, being absent along most of its length. There is a fibrillar sheath, which may or may not be spiral, round the matrix in which the tail fibrils are embedded.

The electronmicrographs were taken with the Siemens Elmiskop I at the Cavendish Laboratory, University of Cambridge. I am indebted to Mr. R. W. Horne for assistance in taking them. This work is supported by the Medical Research Council.

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ISOLATION OF CYTOPATHOGENIC AGENTS FROM THE RESPIRATORY TRACT IN ACUTE LARYNGOTRACHEOBRONCHITIS

BY

A. J. BEALE, M.D., Dip.Bact.*
Research Fellow in Virus Diseases

D. L. McLEOD, M.D.
Poliomyelitis Research Fellow

W. STACKIW, B.Sc.

AND

A. J. RHODES, M.D., F.R.C.P.Ed.
Director

Research Institute, Hospital for Sick Children, Toronto, Canada

[WITH SPECIAL PLATE]

Acute laryngotracheobronchitis is a common syndrome in North America, which is often called croup after the most prominent symptom. It is one of the leading causes for admission to the Hospital for Sick Children, Toronto. Modern methods of treatment have greatly lowered the mortality, which is now negligible, but the aetiology remains obscure. Bacteriological studies have not been very fruitful (Neffson, 1949; Rabe, 1948; Morgan *et al.*, 1956), but both *Corynebacterium diphtheriae* and *Haemophilus influenzae* Type B have been shown to cause a few cases. The lack of a bacteriological cause for most cases has led to increasing support for the idea that a virus may be responsible. Rabe (1948) has discussed the indirect evidence favouring this hypothesis.

During extensive studies of the aetiology of the condition undertaken in Toronto in recent years cytopathogenic agents have been isolated from the tracheal secretion of several patients (Morgan *et al.*, 1956; Beale, McLeod *et al.*, 1957). Chanock (1956) has recently described the isolation of two similar agents from cases of croup. In this paper an account of the investigations in Toronto during the winter of 1955–6 is presented.

Methods

The patients were admitted to the Hospital for Sick Children during October or November, 1955. The disease was sufficiently severe in all cases to raise the possibility of tracheotomy. Tracheal secretion was obtained as soon as possible after operation from all children undergoing tracheotomy. Nasopharyngeal secretion was obtained from the remaining patients by the method devised by Auger (1939). Serum was collected from all the patients soon after admission, and wherever possible a convalescent sample was obtained two to three weeks later. All specimens were stored at −40° C. A full clinical history was taken in each case, and all patients were followed up during convalescence in order to confirm the diagnosis.

Tissue Cultures for Virus Studies

HeLa and human amnion cells were used. HeLa cells were grown in Hanks's solution with 0.5% lactalbumin hydrolysate and 20% human serum. Culture tubes were washed three times in Hanks's solution before use, and then maintained in Earle's solution with 0.5% lactalbumin hydrolysate, 0.1% yeast extract, and 5% horse or rabbit serum. In virus isolation experiments culture fluid was changed about twice a week, in order to keep the cells healthy as long as possible. The human amnion cells were obtained by trypsinization by the method described elsewhere (Beale, Doane, and Ormsby, 1957). They were grown in the same medium as HeLa cells and the same maintenance fluid was used, but, unlike with HeLa cells, no fluid change was required during long periods of maintenance. Specimens were inoculated in 0.1-ml. amounts into two or three tubes containing 1 ml. of maintenance fluid. Cultures were examined daily under the low power of the microscope until control uninoculated cultures started to degenerate.

Serology

Neutralization tests were performed by adding undiluted tissue-culture-fluid virus to serial twofold dilutions of unheated patients' serum. The mixtures were allowed to stand for one hour at room temperature and then inoculated into culture tubes, employing four tubes per dilution. The results were read 48 hours after cytopathogenic effects were noted in virus control cultures. If the cultures were left for longer periods virus tended to break through the sera. Complement-fixation tests were performed by the micromethod devised by Fulton and Dumbell (1949). In order to prevent drying of the drops during performance of the tests a humidified cabinet was used. Haemagglutination tests were made in tubes as described by Chanock (1956), an equal quantity of virus and 0.25% newborn chick cells being used. Chick cells were stored at −20° C. in glycerol citrate as described by Mollison (1954). The tests were read by observing the patterns of sedimented cells after two hours at 4° C.

Results

Fifteen patients (Table I), all between the ages of 6 months and 3 years, were studied. There were 12 males and 3 females, which shows the usual predominance of males (Morgan *et al.*, 1956). Seven patients required tracheotomy and eight recovered without operation. In all cases recovery and convalescence were uneventful. Ten of the 15 patients yielded cytopathogenic agents in tissue cultures, five among the tracheotomized and five among the unoperated patients. In Table II the results of attempts to isolate virus in HeLa and human amnion cells are compared. It will be seen that of the seven tracheotomized patients five yielded a virus, all except for one (which was not tested in human amnion cells) in both cell types. The superiority of human amnion cells for the isolation of these agents is clearly shown by

TABLE I.—*Isolation of Virus from Patients With Acute Laryngotracheobronchitis*

Case No.	Age (Months)	Sex	Tracheotomy	Virus Isolation
1	8	M	Yes	+
2	12	M	Yes	−
3	24	M	Yes	+
4	18	M	Yes	+
5	27	F	Yes	−
6	26	F	No	+
7	13	M	No	+
8	8	M	No	−
9	24	M	Yes	+
10	32	M	Yes	+
11	39	F	No	+
12	17	M	No	−
13	26	M	No	+
14	6	M	No	−
15	8	M	No	+

TABLE II.—*Virus Isolation in HeLa and Human Amnion Cells*

	From Tracheal Secretion			From Nasopharyngeal Secretion		
Case No.:	9	1, 3, 4, 10	2, 5	6, 13	7, 11, 15	8, 12, 14
HeLa cells	+	+	−	+	−	−
Human amnion cells	Not tested	+	−	+	+	−

*On leave from the Public Health Laboratory Service. Now at the Public Health Laboratory, Newcastle upon Tyne.

LORD ROTHSCHILD: THE HUMAN SPERMATOZOON

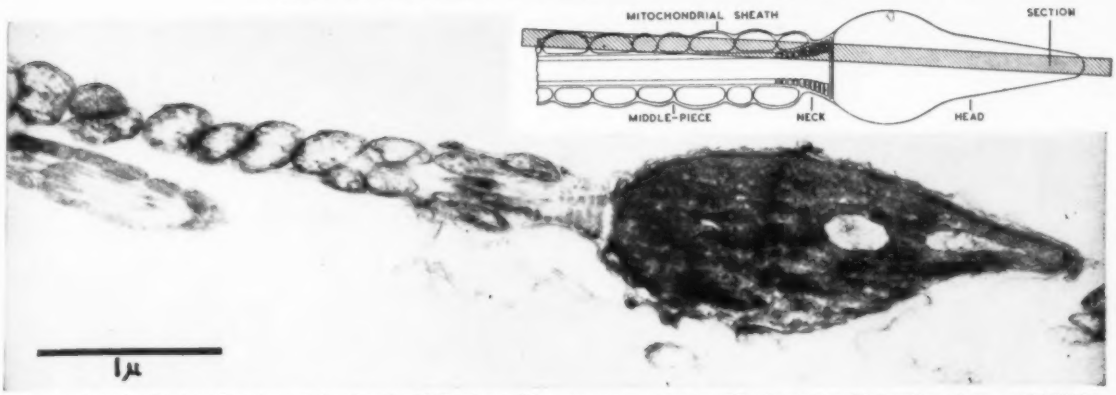


FIG. 1.—Longitudinal section through head and middle-piece of human spermatozoon. (Osmium tetroxide/methacrylate. ×27,500.) Small diagram shows approximate plane of section.

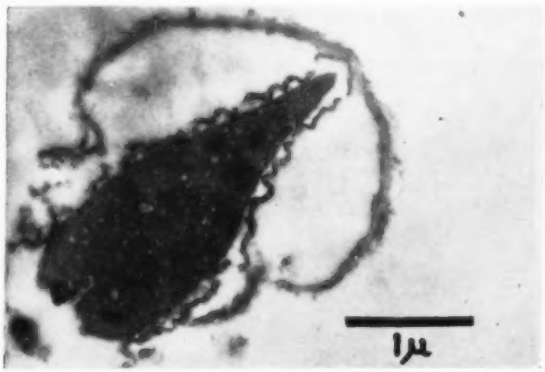


FIG. 2.—Longitudinal section through head of human spermatozoon. Acrosome and enveloping membranes have separated from surface of sperm head. (Osmium tetroxide/methacrylate. ×20,000.)

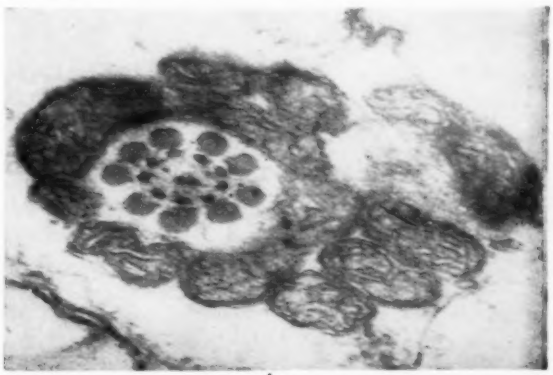


FIG. 3.—Transverse section through middle-piece of human spermatozoon which may be immature. (Osmium tetroxide/methacrylate. ×80,000.)

A. J. BEALE *ET AL.*: ACUTE LARYNGOTRACHEOBRONCHITIS

FIG. 1.—Normal human amnion cells. (Unstained. ×70.)

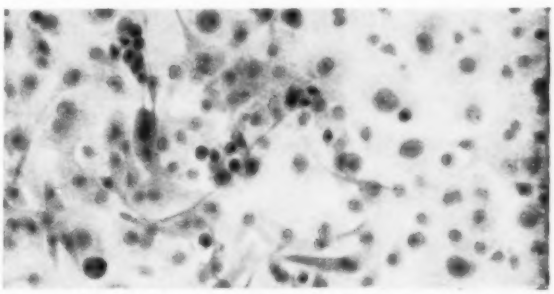


FIG. 2.—Normal human amnion cells. (Haematoxylin and eosin. ×175.)

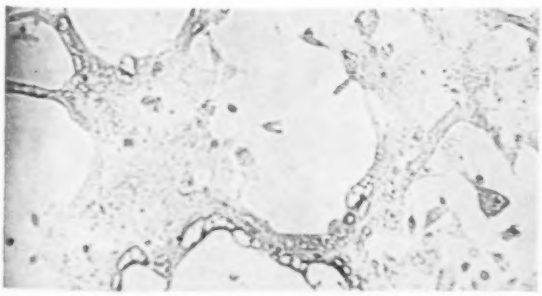


FIG. 3.—Effect of virus from case of laryngotracheobronchitis on human amnion cells. (Unstained. ×70.)

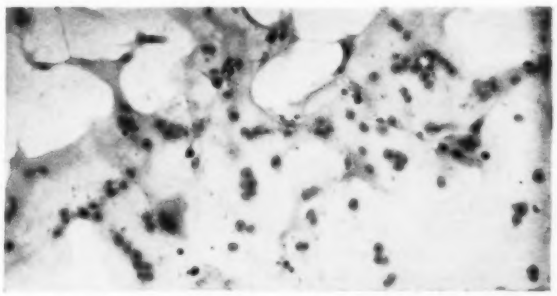
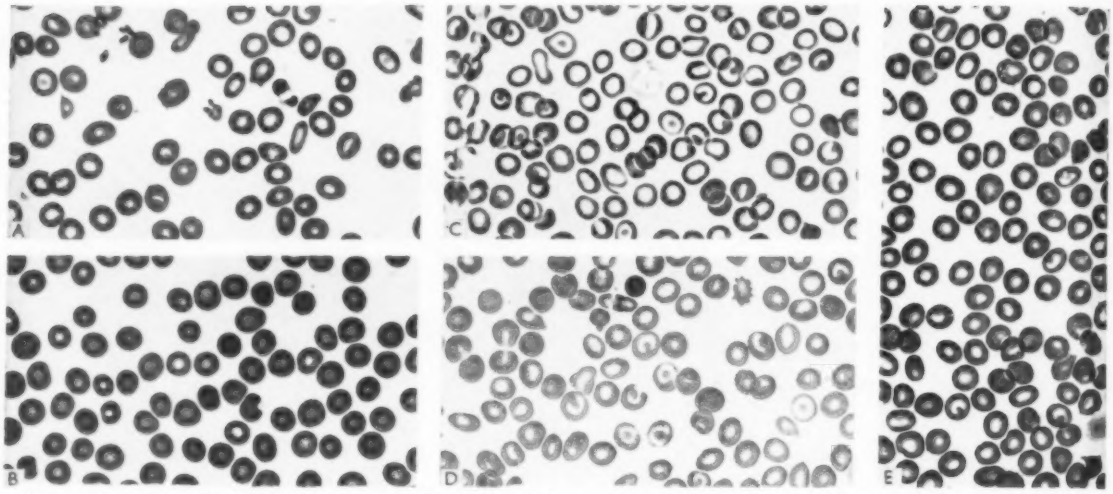


FIG. 4.—Effect of virus from case of laryngotracheobronchitis on human amnion cells. (Haematoxylin and eosin. ×175.)

C. W. H. HAVARD *ET AL.*: THALASSAEMIA MINOR



Appearance of red cells of patient (A), her son (B), her two thalassaemic brothers (C and D), and her normal sister (E). (×500.)

A. H. M. SIDDONS: OIL GRANULOMA OF LUNG

FIG. 1.—Case 1. Radiograph showing lesion in postero-basic segment of left lower lobe.

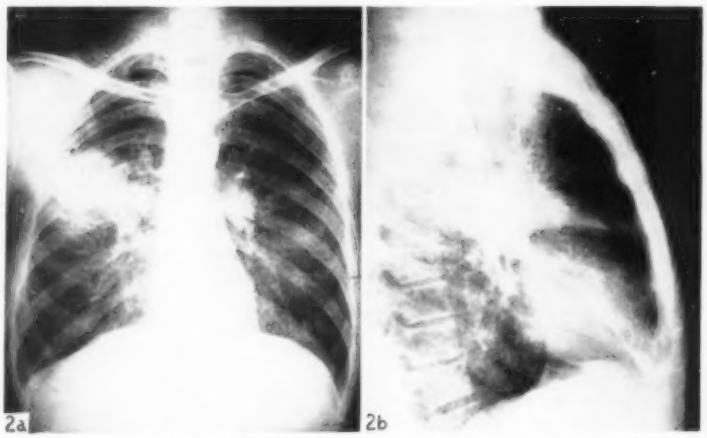


FIG. 2*a*, *b*.—Case 3. Radiographs showing mass in right upper and middle lobes.

F. OSMOND-CLARKE AND M. MURRAY: VAGINAL SMEARS

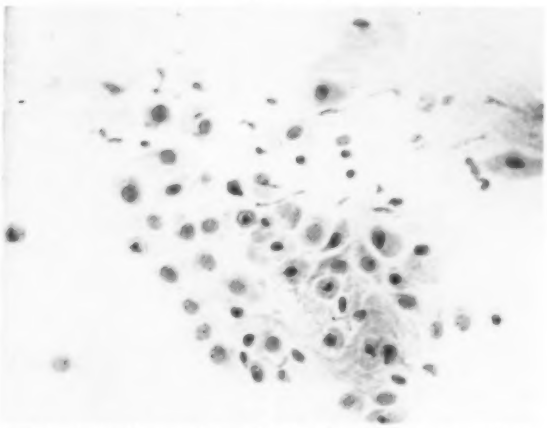


FIG. 1.—Vaginal smear from patient with secondary amenorrhoea, showing marked degree of atrophy of epithelium. (×240.)

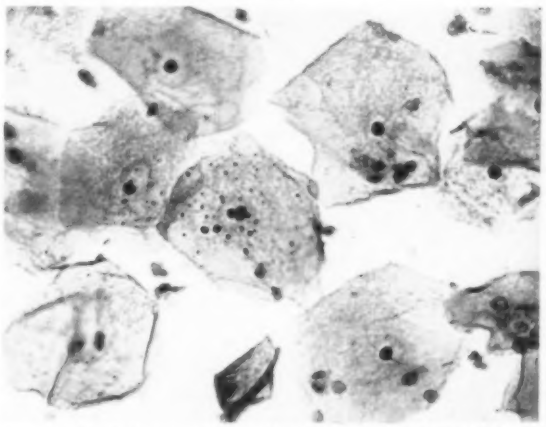


FIG. 2.—Vaginal smear from patient with ovarian agenesis, showing marked oestrogenic activity six months after implantation of 300 mg. stilboestrol. (×240.)

the results for nasopharyngeal secretion. Two patients yielded agents in both types of cells, and three only in human amnion cells. Two did not yield virus. Amnion cells were superior partly because of the greater ease of maintenance of healthy cultures. The agents are slow to produce cytopathogenic effects, taking 17 or more days on primary isolation.

The results of the serum neutralization tests performed on the paired sera from six patients are shown in Table III. It will be seen that all six showed a rise in antibody level during convalescence.

TABLE III.—*Virus Neutralization Tests: Acute and Convalescent Sera Titrated Against Virus Isolation from Patients*

Case No.	Acute Sera		Convalescent Sera	
	Date of Collection	Neutralization Titre	Date of Collection	Neutralization Titre
1	4/10/55	4	14/10/55	64
3	24/10/55	4	12/11/55	64
4	29/10/55	4	5/11/55	32
9	11/11/55	4	19/11/55	32
10	11/11/55	64	21/11/55	1,024
13	14/11/55	4	24/11/55	256

The cytopathogenic effect of these agents is distinctive. The appearance of normal human amnion cells is illustrated in the Special Plate, Figs. 1 and 2. In the unstained preparation (Fig. 1) a clear, almost invisible sheet of cells is shown, in which an impression of the cell outline can be made. In the stained preparation (Fig. 2) the nuclei are prominent, each containing one or more nucleoli. The nuclei are uniformly dispersed in finely granular cytoplasm, but the cell boundaries are not clearly defined. The appearance of infected cultures after one week is depicted in Special Plate Figs. 3 and 4 (strain Manganero from Case 1). There is a loss of cells with vacuolation of the cytoplasm. In unstained preparations the rest of the culture has an amorphous appearance (Fig. 3); Chanock (1956) has likened these changes to a sponge or Swiss cheese. In stained preparations more or less normal-looking nuclei are lined up in columns or aggregated in amorphous cytoplasm (Fig. 4). No intranuclear inclusion bodies have been seen in preparations stained with haematoxylin and eosin after fixation in either Bouin's fluid or a methyl-alcohol–acetic-acid mixture (Doane *et al.*, 1955). The changes in HeLa cells consisted in clumping of cells with loss of the cell walls to give multinucleated giant cells. The changes progressed in both cell types so that finally most of the cells fell off the glass.

These changes are unlike those produced by other viruses studied in this laboratory (poliomyelitis, Echo, Coxsackie, adenoviruses, herpes simplex, and vaccinia). The changes are somewhat similar to those described for measles virus, although no intranuclear inclusions were seen (Enders and Peebles, 1954). They are also similar to those seen in some of the viruses found in normal monkey kidney cells (Hull *et al.*, 1956). However, none of these agents was passed in monkey kidney cells. As an additional control in passage experiments fluids from previous control cultures were also passed in parallel into fresh cultures.

One strain (Manganero) was inoculated into suckling and adult mice, hamsters, and a rabbit without producing any pathogenic effects. The virus did not agglutinate human Group O red cells at room temperature, but, following advice from Dr. Chanock, it was found that newborn chick cells, and to a lesser extent human cells, were agglutinated at 4° C. The characteristics of this haemagglutination are illustrated by the experiment in Table IV. It will be seen

TABLE IV.—*Haemagglutination*

Treatment	Dilutions of Virus					
	5	10	20	40	80	160
4° C. for 2 hours	+	+	+	+	—	—
37° C.	—	—	—	—	—	—
4° C. for 2 hours	+	+	+	+	—	—

that the cells are agglutinated at 4° C., but settle normally again if they are shaken up and allowed to settle at 37° C. This is similar to the behaviour of the influenza group of viruses (myxovirus); however, unlike members of this group, the agents from laryngotracheobronchitis will reagglutinate the cells if these are placed at 4° C. again. During the process of agglutination virus is absorbed from the fluid and subsequently released at 37° C. Although Chanock (1956) has described the use of haemagglutination inhibition titrations for serum antibody, this technique was not used because of the widespread occurrence of non-specific inhibitors.

One strain (Manganero) was sent to Dr. Chanock, who found that it was similar in haemagglutination inhibition tests to the two agents he isolated from cases of croup. He kindly provided monkey antiserum to his Greer strain, and all six of the strains (Nos. 1, 3, 9, 10 and 13, and Greer) subjected to complement-fixation tests gave a titre of 1:40 with this serum.

It was found that both the infectivity and haemagglutinating power of the virus was destroyed by ether.

Discussion

The relationship of these agents isolated from patients to the aetiology of laryngotracheobronchitis remains to be determined by future work. Although they appear to be present in the respiratory tract in a high proportion of cases, and to be associated with an antibody rise during convalescence, no studies were undertaken in Toronto into the incidence of the virus in normal children. Chanock (1956) has presented evidence of widespread past infection with these agents in young adults. It is clear that the agents isolated in Toronto are similar to those isolated by Chanock. Chanock, on the basis of their size, ether sensitivity, and haemagglutination, has provisionally assigned them to the myxovirus group (Andrewes *et al.*, 1955). He has also noted a serological relationship to mumps virus, a virus which also produces giant cells in HeLa cells.

Summary

The isolation of 10 agents in tissue culture from 15 patients with acute laryngotracheobronchitis is described.

Human amnion cells proved superior to HeLa cells for the isolation of these agents.

All six patients tested developed neutralizing antibodies in convalescence.

The cytopathogenic effects are illustrated and some of the properties described. These are similar to those of the influenza–mumps–N.D.V. group of viruses.

There is suggestive evidence that the agents actually caused disease in the patients studied, but more work is required to establish this beyond doubt.

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THALASSAEMIA MINOR IN AN ENGLISHWOMAN

BY

C. W. H. HAVARD, B.M., M.R.C.P.

H. LEHMANN, M.D., Ph.D., F.R.I.C.

AND

RONALD BODLEY SCOTT, D.M., F.R.C.P.

St. Bartholomew's Hospital

[WITH SPECIAL PLATE]

Thalassaemia is a hereditary hypochromic microcytic anaemia for which there exist a number of synonyms—microcythaemia; hereditary leptocytosis; Mediterranean, Cooley's, and target-cell anaemia. In Europe it has hitherto been regarded as the prerogative of the Mediterranean races, although there have been reports of cases from Germany. The purpose of the present paper is to record an example in a woman of pure English stock.

The underlying defect in the disease is an interference with the synthesis of normal adult haemoglobin (Rich, 1952). Homozygous and heterozygous forms occur, but the first is commonly severe, while the second is often without symptoms. In consequence their relationship was not appreciated until it was established that the parents of children with Cooley's anaemia, or thalassaemia major, themselves exhibited a mild form of the disease, or thalassaemia minor (Gatto, 1941; Wintrobe, 1942; Dameshek, 1943).

Haematological Features

The peripheral blood is marked by microcytosis due to reduction in the thickness of the red blood cells, which confers upon them the characteristic "target" appearance. The hypochromia depends rather upon a low haemoglobin content of the cells than upon a low saturation. The red blood cell count may not be reduced and, indeed, may exceed normal. In the film anisocytosis, poikilocytosis, and punctate basophilia are to be noted as well as the target-cell deformity; normoblasts are common when anaemia is profound. The flattened red cells have an increased resistance to hypotonic solutions, consequently their osmotic fragility is reduced, although mechanical fragility is increased and their span of life shortened. The haemoglobin content of the red blood cells is so low that the increased rate of their destruction may not lead to a significant rise in serum bilirubin level or increase in stercobilinogen excretion. The bone marrow undergoes a normoblastic hyperplasia.

Foetal haemoglobin (Hb-F) has normally disappeared from the red blood cells by the age of 6 months; but the ability to form this pigment may be retained in any anaemia which develops in early infancy, and it is present in increased amounts in thalassaemia. Haemoglobin A_2 (Hb-A_2), a fraction of normal adult haemoglobin (Hb-A) resembling haemoglobin E in its electrophoretic properties (Kunkel and Wallenius, 1955), is normally present in quantities not exceeding 3%. In thalassaemia this proportion may rise to 15%.

Although the hypochromic microcytic anaemia of thalassaemia resembles that of iron deficiency, the level of iron in the serum is normal or high and there is no response to iron medication.

Study of the patient's relatives is essential before a diagnosis of thalassaemia can be established. The clear-cut genetic differences between the homozygous and heterozygous forms do not extend to the clinical features because of the variable penetrance of the thalassaemia gene. Although the heterozygous state is usually asymptomatic, it may occasionally be associated with profound anaemia, splenomegaly, and skeletal changes.

In thalassaemia minor the low mean corpuscular haemoglobin is often combined with an increase in the red blood cell count which maintains the circulating haemoglobin concentration at a normal level. The patient is thus preserved from significant anaemia unless an additional load is imposed by haemorrhage or haemolysis. In these circumstances a minor loss of blood may result in severe anaemia which the already extended bone marrow cannot repair. Such circumstances led to the discovery of thalassaemia minor in the present instance.

Case Report

The patient, a housewife aged 48 years, was of pure English stock. Her family had been farmers in East Anglia for many generations and there had been no known intermarriage with foreigners in the past. Her mother was said to have been anaemic, although she lived to an advanced age.

The patient was referred to St. Bartholomew's Hospital in March, 1957, for investigation of a hypochromic anaemia which had proved refractory to treatment with iron. Three years previously she had been admitted to another hospital with a haematemesis; after a second haemorrhage on the day following admission the haemoglobin had fallen to 6.9 g. per 100 ml. She had made a satisfactory recovery, but even after intensive treatment with iron by mouth and by intravenous injection the haemoglobin level had not risen above 10.0 g. per 100 ml. A year later the figure had been 9.4 g. per 100 ml., and after further treatment with iron for a month, 9.8 g. per 100 ml. At this time physical examination had been normal. The serum bilirubin had been raised to 1.4 mg. per 100 ml., but liver function had been intact and there had been no radiological evidence of gastro-intestinal disease. Three months later the haemoglobin reading was still only 10.4 g. per 100 ml.

On admission to St. Bartholomew's Hospital 10 months later she was pale but well nourished. The spleen and liver were impalpable and there were no physical signs of disease apart from slight cardiac enlargement. The details of her blood count are set out in the Table. The white cells numbered 8,100 per c.mm. (neutrophils 62%, eosinophils 1%, basophils 1%, lymphocytes 34%, monocytes 2%), and platelets 260,000 per c.mm. Films of the bone marrow showed intense normoblastic hyperplasia. The serum bilirubin level was 0.7 mg. per 100 ml., and the mean daily faecal urobilinogen excretion 100 mg. Estimation of the serum iron gave a figure of 120 µg. per 100 ml. Osmotic resistance of the red blood cells was increased (see Chart); the Wassermann reaction and the direct and indirect Coombs tests were

Haematological Findings in the Patient, Her Son, and Three Siblings

	Patient	Patient's Son	Brother of Patient	Brother of Patient	Sister of Patient
Haemoglobin (g. per 100 ml.)	11·2	13·9	12·7	12·4	14·5
Red cells (millions per c.mm.)	5·12	4·42	4·80	5·08	5·08
Cell volume (%)	35	43	37	40	45
M.C.V. (cubic µ)	68	97	77	79	89
M.C.H. (µµg.)	21·9	31·5	26·6	24·4	28·5
M.C.H.C. (%)	32·0	32·3	34·3	31·0	32·2
M.C.D. (µ)	7·6	8·0	7·6	8·1	7·8
M.C.A.T. (µ)	1·5	1·9	1·7	1·5	1·9
Reticulocytes (%)	3·4	0·4	0·7	0·6	0·4
Target cells	+	−	++	++	−
Stippling	+	−	+	+	−
Osmotic fragility (range in % NaCl)	0·48–0	0·45–0·35	0·40–0·10	0·40–0·15	0·45–0·30
Foetal haemoglobin (%)	3·1	Nil	6·1	5·4	Nil
Haemoglobin A_2 (% of A)	5·1	2·1	8·5	5·8	1·9
Serum iron (µg. per 100 ml.)	120	204	124	150	140

negative. Results of liver function tests were normal. There was no radiological evidence of oesophageal varices or of gastro-duodenal disease.

Study of the patient's haemoglobin revealed 3.1% alkali-resistant pigment (Hb-F). On electrophoresis an increase in Hb-A_2 was noted in the unstained paper strip (reproduced herewith). On staining with a protein dye and subsequent elution, colorimetry showed the proportion of Hb-A_2 to be significantly raised to 5.1% of the total Hb-A.

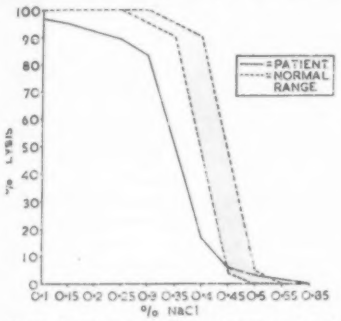
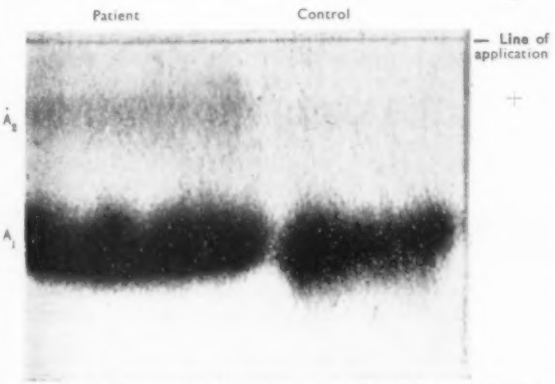


Chart showing osmotic resistance of red blood cells.

The abnormalities demonstrated in this patient's blood may be summarized as an iron-resistant hypochromic microcytic anaemia with target cells, basophilic stippling, and reticulocytosis; increased osmotic resistance of the red blood cells; the presence of Hb-F and an increase in the Hb-A_2 fraction; and a normal level of serum iron. These results provided evidence that the patient had thalassaemia minor, and the diagnosis was conclusively established by the demonstration of similar changes in the blood of two out of three siblings, neither of whom had any symptoms or was conscious of being anaemic (see Special Plate). The patient's only son was normal and thus afforded proof of her heterozygous state (see Table).



Paper electrophoresis of haemoglobin of patient and of a normal control. The strip has not been stained, but even so a band of haemoglobin is visible in the position of Hb-A_2 in the case of the patient but not in that of the control.

Discussion

Reports of thalassaemia in persons of English descent are few. An example was recorded by Bywaters as long ago as 1938. The patient died during the war, but, by the courtesy of Professor Bywaters, we have been in touch with her parents and the blood of neither has the features of thalassaemia. It seems unlikely, therefore, that the case would have met present-day diagnostic requirements. Thalassaemia was noted in a family of Scottish immigrants in Canada (Israels, Suderman, and Hoogstraten, 1955), but there was evidence of illegitimacy in one of the propositus children, and, as they came from a Scottish port, it is probable that the gene was of recent and irregular acquisition. Israëls and Turner (1955) have reported "target-cell anaemia" in two young Englishwomen without Mediterranean ancestry. In both cases the essential criteria required for the diagnosis of thalassaemia were present, and family studies provided supporting evidence.

It seems probable that this disorder is less rare in persons of English stock than these scanty reports would suggest. The discovery of another affected family underlines the importance of considering the possibility of thalassaemia when confronted by a patient with refractory hypochromic anaemia.

Summary

The case is reported of a middle-aged woman of East Anglian farming stock in whom a refractory hypochromic anaemia was shown to be due to thalassaemia minor. Evidence of this disorder was also found in her two brothers, but not in her sister or her son.

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OIL GRANULOMA OF THE LUNG

REPORT OF THREE CASES

BY

A. H. M. SIDDONS, M.Chir., F.R.C.S., M.R.C.P.

Assistant Director, Surgical Unit, St. George's Hospital, London

[WITH SPECIAL PLATE]

The condition of lipoid granuloma of the lung was first described in 1925 by Laughlen. The large numbers of reports in the American literature on the subject have recently been reviewed by Buechner and Strug (1956) and also by Steinberg and Finby (1956). Most of the cases reported have been due to collections of liquid paraffin in patients taking this substance by mouth or as nasal drops or sprays. However, mineral oils are not the only source of the trouble, vegetable and animal oils and various fats having also been indicted. In addition there is a special group of cases due to poppy-seed oil used for bronchography.

These exogenous oil and fat granulomas must be distinguished from lesions containing endogenous fatty substances occurring in association with bronchial obstruction and generalized disturbances of fat metabolism. In this paper are reported three cases of lipoid granuloma believed to be of exogenous origin and forming localized tumour masses clinically resembling carcinoma of the bronchus.

Incidence

From the few reports of such granulomas which have appeared in the literature in this country (Paterson, 1938; Rewell, 1947; Belcher, 1949; Nelson, 1954) it might be concluded that the condition is a great rarity, but the three cases here described occurred in the author's practice in just over one year, suggesting that the condition must be fairly common. The cases reported in the literature show that, though the disease may occur at any age, it is fairly common in babies with feeding disturbances, when milk may reach the lungs, where its fat content tends to remain, as it is much more slowly removed than the other constituents. At the other extreme of life it becomes more common again, so that in a hospital treating the aged with such conditions as neurological disorders (especially Parkinsonism), cerebrovascular conditions, and rheumatoid arthritis it has been reported in as many as 14.6% of inmates (Volk *et al.*, 1951). This high incidence is presumably associated with disturbance of swallowing; the

condition has been reported many times in association with achalasia of the cardia (Belcher, 1949 ; Steinberg and Finby, 1956).

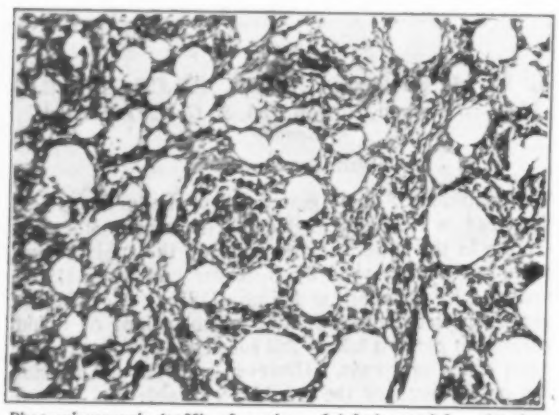
Diagnosis

The symptoms are often minimal, though some cough and breathlessness are common and occasionally there is haemoptysis. These patients, however, often develop lung infections in association with the oil granuloma, and it is in this way that most of such cases come to light.

The recognition of oil granuloma may avoid an unnecessary operation, though even at operation the diagnosis from carcinoma may be very difficult, but if made will allow of a less extensive resection than that designed for malignant disease.

Case 1

A man aged 72 reported sick because of recent cough with some dyspnoea. He was a heavy pipe smoker. Examination revealed abnormal signs at the base of the left lung, but no finger-clubbing and no other significant disease. Radiography (Special Plate, Fig. 1) showed a lesion in the postero-basic segment of the left lower lobe. No abnormality was seen bronchoscopically. At operation an exceptionally hard "cobblestone" mass was felt in the lower lobe and the lobe was removed. The specimen contained a firm, fairly well demarcated greyish mass measuring 5.5 by 4 by 2.5 cm. in the lateral basal segment. The bronchi were normal. Microscopical examination showed a mesh of dense fibrous tissue containing numerous large vacuoles of lipoid material ; the histological appearance is shown in the accompanying photomicrograph. A foreign-body giant-cell reaction was present in some areas, and there were similar changes in the hilar lymph nodes.



Photomicrograph (×50) of section of left lower lobe, showing dense fibrous tissue containing large vacuoles of lipoid material (Case 1).

Subsequent questioning elicited that the patient habitually took liquid paraffin as an aperient. He made an uneventful recovery, and during the eighteen months since operation he has had no further chest symptoms, though he has aged considerably, becoming partly senile.

Case 2

A woman aged 56. *X*-ray examination one month before operation showed a mass confined to the right middle lobe. She was almost symptom-free, though she had a dry cough which she attributed to smoking. In the course of the month's observation she had a pyrexial illness, which was treated with penicillin. No abnormality was seen on bronchoscopy. At operation a hard, rounded lesion about 1½ in. (3.75 cm.) in diameter was found. Examination of a frozen section confirmed the diagnosis. The middle lobe only was removed. The specimen contained a clearly defined, very firm greyish mass measuring 3.6 by 2.4 by 2.2 cm. The bronchi were normal. Microscopical examination showed a dense fibrous-tissue meshwork enclosing large droplets of lipoid material, a few small areas of active inflammation with giant-cell reaction were present.

The post-operative course and the six months since operation have been uneventful. The patient denies having taken liquid paraffin by mouth or using nasal drops or sprays at any time.

Case 3

A man aged 41, who gave a history of polyneuritis for six years. For the first two of these he was in hospital and suffered from dysphagia ; he also had two attacks of pulmonary infection followed by breathlessness. A year before the lung condition was found his dysphagia was shown to be due to achalasia of the cardia ; a myotomy of the cardia (Heller's operation) was performed, completely relieving the dysphagia. However, a barium-meal examination two months after the operation showed some retention in the oesophagus 20 minutes after swallowing ; the contour of the oesophagus appeared normal.

The first chest radiograph was taken one month before his admission, and revealed a mass in the right upper and middle lobes, which had enlarged considerably by the time he reached hospital (Special Plate, Figs. 2a and b). He then had a slight productive cough and was breathless on exertion. His sputum was not examined for fat, and bronchoscopy revealed no abnormality. The large-sized shadow in association with a normal bronchoscopic appearance led to discussion of lipoid granuloma as a possible diagnosis, for had there been a carcinoma one would have expected to see a lesion with the bronchoscope. At operation a large, hard, lobulated tumour mass was seen in the right upper lobe with a fingerlike process extending into the middle lobe. Frozen section at operation established the diagnosis of lipoid granuloma, though even this did not exclude the possibility of a small carcinoma within the mass. The right upper lobe only was removed. The specimen contained a well-defined, firm area, 10 by 6 by 4.5 cm., in the posterior segment, the mass consisting of grey, semitranslucent tissue. The bronchi appeared normal. Microscopical examination showed the presence of very numerous droplets of lipoid material. In some areas there was an intense, acute inflammatory reaction with numerous giant cells around the lipoid, in others the lipoid material was surrounded by dense fibrous tissue. There were similar changes in the mediastinal lymph nodes.

The post-operative course was complicated by a bronchopleural fistula with an apical air-space, which did not become infected. Two months after operation a four-rib thoracoplasty was performed to close the persistent pleural space, and within a few weeks this appeared to be completely obliterated. Later a localized shadow was visible in the apex of the left lower lobe, and twelve months after operation this shadow had become much larger. It is presumed that the shadow represents a new area of lipoid granuloma in the lower lobe. The patient remains symptom-free except for a minimal dry cough. Questioning after the diagnosis was suspected reveals no history of the use of liquid paraffin.

Discussion

In Case 1 a history of the use of liquid paraffin over many years fits in with the final diagnosis, though there was no disturbance of swallowing. In Case 2 no such history was obtained even on cross-examination after the diagnosis was established. No doubt oil or fat capable of producing the lesion was included in the diet, but once again there was no explanation of why it reached the lungs. In Case 3 the history of achalasia of the cardia is characteristic, and, though no oily medicaments were taken, the inhalation of food from the abnormal oesophagus can be presumed, for it has been shown to be a common event in such cases. Owing to the absence of lung symptoms a radiograph was not taken until some months after the Heller operation. The features which are more difficult to explain are the increase in size of the lung shadow over the months following the operative relief of the achalasia, and its recurrence after removal of the upper lobe, when only a minimal lesion was

palpable in the middle lobe. One is forced to the conclusion that the 20-minute delay in emptying the oesophagus seen after the barium meal is significant, and that during sleep some of the oesophageal contents spilt over into the lung, it being well known that in patients with achalasia an advanced degree of food retention in the oesophagus may occur without their noticing it.

The clinical and *x*-ray findings in these three cases suggested a carcinoma, but in each of them one would have expected the carcinoma to be visible at bronchoscopy. Indeed, after the experience of the first case the negative bronchoscopic findings led to doubt of this diagnosis, and the exceptionally hard and lobulated feel of the mass at operation helped to confirm the suspicion that the lesions were oil granulomas. At two of the operations it was possible to obtain further evidence by frozen sections of a biopsy taken from the lesion.

The presence of fatty globules in the sputum, as was found in one of these cases, is strong evidence of oil granuloma and is undoubtedly the most helpful pointer to the diagnosis. Radiologists have described the *x*-ray appearances of these lesions in great detail, and may be able to suggest the diagnosis when the lesions are multiple and occur in the "aspiration" areas of the lungs, but there are no radiological features which allow certain distinction from carcinoma or the "pneumonias." There are many oily substances which may reach the lungs and give rise to this granulomatous condition, varying from the very inert mineral oils (for example, hydrocarbons such as liquid paraffin) to partially unsaturated vegetable and animal oils and fats (cod-liver oil, butter fat, etc.) (Kaplan, 1941). Staining with the fat stains in common use in histology and examination with polarized light (Wagner *et al.*, 1955) may go some way towards the identification of the substance, but there are many difficulties in analysing the small quantities of substance available, and it is fortunate that such exact analysis is rarely necessary.

The histology described in the case reports is typical of the condition. It has been suggested that the acute reaction is more pronounced when the foreign material contains unsaturated fats. In all cases of long standing fibrosis dominates the picture, but many oily globules remain enmeshed in the fibrous tissue (Pinkerton, 1928; Ikeda, 1937).

Summary

Three cases of oil granuloma of the lung are described. Each simulated, both clinically and radiologically, a bronchial carcinoma and was treated by resection. The condition usually results from taking liquid paraffin by mouth or in nasal sprays and is often associated with disturbances of swallowing: thus it is seen in infants with feeding difficulties and in adults with neurological disorders and diseases of the oesophagus. Once it has been suspected it may be diagnosed by finding fatty globules in the sputum.

In one of the cases reported liquid paraffin had been taken for many years. Another patient had achalasia of the cardia, which had been treated surgically. In the third case there was no explanation of the origin of the granuloma. One of the cases was most unusual in that the lung lesion appeared to be progressive after removal of the grossly affected lobe.

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SOME CLINICAL APPLICATIONS OF VAGINAL SMEARS IN GYNAECOLOGICAL ENDOCRINOLOGY

BY

FREDA OSMOND-CLARKE, M.B., Ch.B.
Hon. Clinical Assistant, Endocrine Department, Chelsea Hospital for Women, London

AND

MOIRA MURRAY, M.B., Ch.B., D.P.H.
Research Assistant, British Empire Cancer Campaign

[WITH SPECIAL PLATE]

The use of the vaginal smear as a method for studying ovarian function is based on the fact that the structure of the vaginal epithelium, like that of the endometrium, is specifically influenced by the ovarian hormones. In 1847 Pouchet published his classic book in which he described the cellular picture of vaginal fluid and its changes during the human menstrual cycle. This work appears to have been forgotten, although in the late nineteenth and early twentieth century several investigators were using the vaginal-smear technique in animal experiments (Lataste, 1893; Stockard and Papanicolaou, 1917; Allen and Doisy, 1923). Later it was again applied to the study of the human menstrual cycle (Papanicolaou, 1933), but it was not until 1936 that Papanicolaou and Shorr recognized its value in relation to the sex hormones.

Since 1943 the clinical application of vaginal cytology has been well established in North and South America by Papanicolaou and Traut (1943), Shorr (1945), and De Allende and Orías (1950). In Belgium Pundel (1950, 1952) and Pundel and Van Meensel (1951) published their very extensive studies on this subject, including the value of vaginal cytology in pregnancy, and more recently we are informed that in Denmark and Sweden the vaginal-smear technique has become a routine procedure in the leading gynaecological endocrine units, though it is still rarely used in this country except for the diagnosis of cancer.

Present Study

From our preliminary work in the Endocrine Department at Chelsea Hospital for Women, where one of us (M. M.) is investigating the possible relationship between oestrogen and uterine carcinoma, we believe that vaginal cytology in experienced hands can be of value in assessing ovarian function. In many patients it is advisable to study daily smears over a period of four to six weeks, and we have found that the majority of patients after instruction are able to take their own smears satisfactorily.

Our observations are based on vaginal smears taken from 110 patients who were attending Dr. P. M. F. Bishop's endocrine clinic and 40 patients attending Mr. J. B. Blaikley's cancer follow-up clinic at the Chelsea Hospital for Women. In the latter case only single smears were taken, while from the others either periodic or daily smears were obtained.

Method of Taking and Examining Smears

The vaginal smear is obtained by aspirating the secretion from the posterior fornix of the vagina. For this purpose we use a "pyrex" glass tube of 5 mm. internal diameter and approximately 6 in. (15 cm.) in length; one end is

slightly angulated and a strong rubber bulb is attached to the other end. With the bulb compressed the dry tube is gently inserted into the posterior fornix of the vagina; the bulb is then released and the tube withdrawn, thus avoiding contamination from the lower third of the vagina. Some of the secretion in the tube is removed with a small rounded stick and lightly rolled on to a dry slide. We use slides with a ground-glass end on which the name and date can easily be written in penicil. While the secretion is still moist the slide is placed in a "polythene" jar containing a fixative of equal parts of ether and alcohol. We would like to stress that smears should be taken before the patient has been examined or douched.

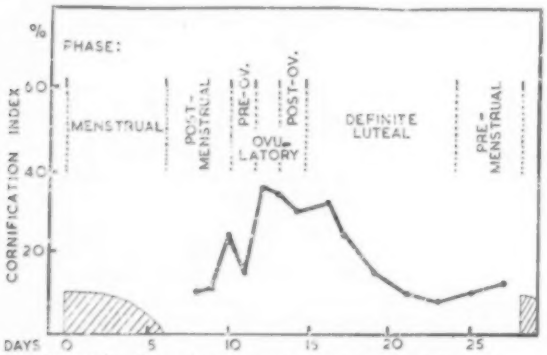
There are many methods of staining vaginal smears, but the techniques of Papanicolaou and of Shorr are the two that are in most constant use to-day. The former is more or less universally employed for detecting malignant cells of the genital tract, while it is considered that the latter gives a more sensitive picture of the influence of hormones on the vaginal epithelium. We have had very satisfactory results with the single differential stain now used in Shorr's clinic in New York (personal communication).

Proportional Parts		
12	Biebrich scarlet	0·3 g.
4	Orange G	0·1 g.
1	Aniline blue	0·025 g.
3	Fast green FCF	0·075 g.
10	Phosphotungstic acid	0·25 g.
10	Phosphomolybdic acid	0·25 g.
	Ethyl alcohol (50%)	100 ml.
	Glacial acetic acid	1 ml.

Cellular Content of Vaginal Fluid

The principal cells found in vaginal smears are: (1) cornified squamous epithelial cells; (2) pre-cornified squamous epithelial cells; (3) intermediary epithelial cells; (4) large basal epithelial cells; and (5) small basal epithelial cells. In general, the percentage of cornified squamous cells varies in proportion to the amount of oestrogen being utilized in the body and is reported as the cornification index. Conversely, the percentage of basal cells varies with the degree of atrophy of the vaginal epithelium. There are, of course, many variations between these two extremes. In addition, there are characteristic patterns of cells which are seen in different phases of the normal cycle, some of which may be produced by hormonal treatment. Many of these are recognizable only after considerable study and experience and are therefore not easily described briefly. However, for those who are interested we would recommend the work of De Allende and Orías (1950).

One method of recording the functional state of the ovaries by means of the vaginal smears is to plot graphically the daily percentages of each type of cell. Briefly, the curve shown by the cornified cells is the most indicative of ovarian activity and is known as the cornification curve. For simplification this is the only curve appearing in the graphs reproduced here. The curve of a normal ovulatory cycle is shown in Graph 1.



GRAPH 1.—Normal ovulatory cycle in a woman aged 22.

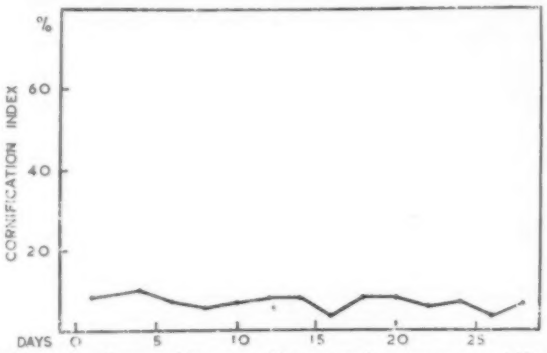
Clinical Applications

Basing our observations on the work of Shorr (1945) and De Allende and Orías (1950), we consider the study of vaginal smears to be of value in amenorrhoea, primary and secondary, in the management of the menopause, and in infertility; also as a therapeutic guide, and to detect the presence or absence of oestrogen in patients with uterine carcinoma.

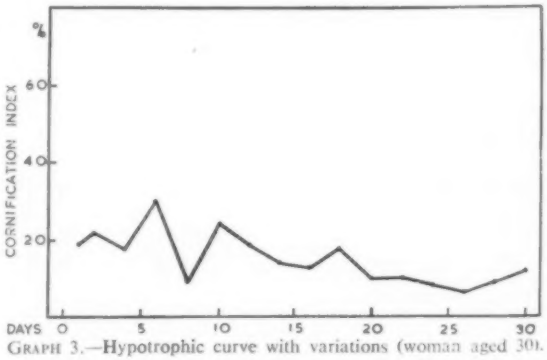
Amenorrhoea

In both primary and secondary amenorrhoea the degree and character of the ovarian dysfunction may vary greatly, so for the purpose of this study both types have been classed together. It is possible to recognize at least four distinct types of smear.

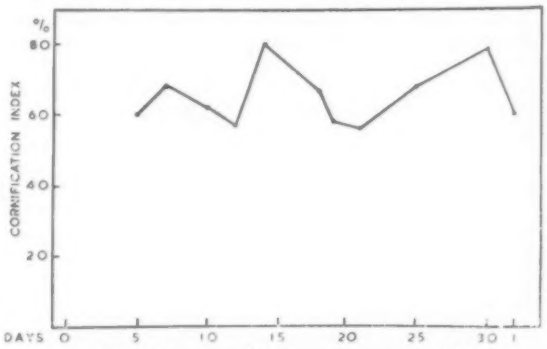
1. *Atrophic.*—This type of of smear is composed chiefly of basal cells which appear in flat strips or groups and are rarely discrete; an occasional squamous cell is seen (Special Plate, Fig. 1). It is found in patients with ovarian agenesis, in old women many years after the menopause, and in some cases of secondary amenorrhoea in which urinary gonadotrophins are not demonstrable. As would be expected, the prognosis



GRAPH 2.—Hypotrophic curve without variations (woman aged 28).



GRAPH 3.—Hypotrophic curve with variations (woman aged 30).



GRAPH 4.—Hypertrophic curve (woman aged 42).

in the last type is poor and worsens in proportion to the duration of the amenorrhoea.

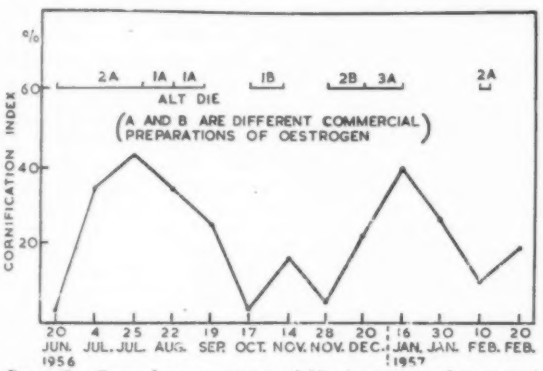
2. *Hypotrophic Without Variations* (Graph 2).—This is a smear showing all types of cells, which are generally smaller than normal but without any significant day-to-day changes, and indicates sub-normal rather than absent ovarian function.

3. *Hypotrophic With Variations* (Graph 3).—This group presents a fluctuating type of vaginal smear with varying degrees of cornification. Normally it is limited to the secondary amenorrhoeas, but may occur in such cases as delayed puberty or where the uterus is rudimentary or absent. These episodes of ovarian activity may be irregular or show a cyclical tendency; in the latter case, according to Shorr (1945), the prognosis is reasonably good. We find this group as a whole shows many variations, and further detailed study is required to enable subdivision into categories of more prognostic value.

4. *Hypertrophic* (Graph 4).—This is the least common, but may be found in patients who have a previous history of heavy bleeding. This type of smear shows a persistently high degree of cornification—a picture one would expect to find during a period of amenorrhoea in a patient suffering from metropathia haemorrhagica or in patients with an oestrogen-secreting cyst or tumour of the ovary.

Management of Menopause

The main function of the vaginal smear is to serve as a base-line for evaluating therapeutic progress (Graph 5). Although the smear is known to show individual variations,



GRAPH 5.—Curve from woman aged 38, three years after natural menopause, showing response to oestrogen administration.

it is a valuable index regarding (*a*) the relative response of individual patients to various types of oestrogen preparations; (*b*) any correlation between particular symptoms and the oestrogen deficiency at that period; (*c*) inadequate dosage; and (*d*) the question whether symptoms have another origin when they persist in the presence of a full oestrous smear.

Infertility

Study of one or two consecutive cycles will indicate whether ovulation has taken place or not. Admittedly this can usually be ascertained more simply from a record of the basal temperatures, if these are correctly taken, but where the cycles are anovular it is frequently possible to obtain further information from a study of the vaginal smears. Some may show a cornification curve similar to that obtained in an ovulatory cycle but without the characteristic post-ovular changes. Others may show evidence of a more marked abnormality, but at present there is, so far as we know, little work being done in this field, and the significance of the various deviations is difficult to assess.

Where infertility is due to the male partner and artificial insemination is recommended it has been suggested that a study of the vaginal-smear picture will increase the accuracy with which the subsequent ovulatory peak is selected.

As a Therapeutic Guide

(*a*) *Menopause.*—This has already been mentioned in connexion with the management of the menopause, where we have found periodic vaginal smears of immense value.

(*b*) *Implantation.*—This method of hormone therapy was first introduced in the human subject by Bishop (1938) and has now become a recognized practice where a prolonged action of oestrogen or progesterone is required—for example, oestrogen in patients with ovarian agenesis, and progesterone in early pregnancy where there is a history of frequent miscarriages. Information regarding the period of activity of these implants may be obtained from the vaginal-smear picture (Special Plate, Fig. 2).

(*c*) *Androgens.*—Where androgen therapy is used to counteract the effect of excessive oestrogen it is possible to assess its efficacy by vaginal smears. In this way it is easier to avoid inadequate or excessive dosage in the early stages of treatment.

(*d*) *Stimulative Therapy.*—Results of attempts to stimulate ovarian activity by the administration of gonadotrophins have so far been generally disappointing in this country. In certain selected patients small stimulatory doses of deep *x*-ray therapy have been applied to the pituitary and/or ovary. From the eight cases we have studied we have been able to observe whether or not the ovaries have shown any response to this form of therapy, and for the moment have divided the results into the following three groups: (1) no ovarian response—3 cases; (2) some ovarian response but insufficient to re-establish menstruation—3 cases; (2) restoration of menstruation—2 cases.

Discussion

In gynaecological endocrinology information regarding ovarian activity is essential for accurate diagnosis and treatment. Unfortunately, the various biochemical assays known at present are more applicable to research projects and are not readily available to the clinician in this country. It is therefore interesting to learn from the recently published work of Young, Bulbrook, and Greenwood (1957) that they have found such a close correlation between urinary oestrogen estimations and vaginal cytology. In our experience Shorr's differential stain for vaginal smears gives the most information regarding hormone activity, and we suggest it should be employed as a standard technique for gynaecological endocrine work. This would make it possible to evolve a more universal method of recording the condition of the smear in terms acceptable to endocrine cytologists and which clinicians could understand.

During this study we have been impressed by the anomalies and individual variations we have encountered. Indeed, there are patterns of cells which, in the light of present knowledge, are inexplicable. Further research in close association with the biochemist and clinician are obviously required before the full significance of vaginal cytology will be understood. In fact, it has many potentialities and may even find a useful place in the study of hormone-dependent cancer.

Summary

In experienced hands vaginal cytology is a useful method of assessing ovarian function. Like all other present methods of observing ovarian function, vaginal cytology has its limitations, but it has the advantages of being simple, inexpensive, and non-traumatic, and does not require the patient's admission to hospital or the use of laboratory animals. Furthermore, it permits a continuous rather than an isolated study of ovarian function. Clinically, it is of value in amenorrhoea to assess the degree and character of ovarian dysfunction, in the management of the menopause, and in infertility. It is also useful as a therapeutic index, and in detecting the presence or absence of oestrogen in cases of uterine carcinoma.

The technique of taking vaginal smears and a method of staining them for examination are described. A short account of the cells found in vaginal smears is given.

We would like to thank Dr. P. M. F. Bishop for his help and permission to study his patients. We also wish to thank Mr. J. B. Blaikley and Mr. G. Wynn Williams for access to their patients, and Mr. R. de Vere, Mr. C. A. Simmons, and Mr. J. Mander for their kind co-operation. We are very grateful to Dr. Magnus Haines, director of pathology, and his photographic department for their help and advice, and are indebted to Sister Boyce, the sister in charge of out-patients, and Miss S. A. Lomax for their assistance.

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DIFFICULTIES ASSOCIATED WITH BREAST-FEEDING

A STUDY OF 106 PRIMIPARAE

BY

F. E. HYTTEN, Ph.D., M.B.

JESSIE C. YORSTON, M.D.

AND

A. M. THOMSON M.B., B.Sc., D.P.H.

Obstetric Medicine Research Unit (Medical Research Council), Midwifery Department, University of Aberdeen

Medical students and nurses are usually taught that breast-feeding is best for the baby and satisfying for the mother; it is tacitly assumed, and occasionally affirmed, that such a "natural" process can be successfully undertaken by most mothers who are keen to do so.

Nevertheless, breast-feeding seems to be declining. Recent surveys in widely separated areas of the United Kingdom show that only about one-third of mothers are breast-feeding by the end of the third month. The rate at this time is higher in the upper than in the lower social classes (Ross and Herdan, 1951; Douglas, 1950; Westropp, 1953; Spence *et al.*, 1954; Hytten and Thomson, 1955).

Several attempts have been made to determine why individual mothers give up breast-feeding prematurely. Most of the studies have been retrospective and based either on routine clinical records or on special interviews with the mothers, sometimes long after the event. In several studies of breast-feeding failure, a definite cause was not established in from 40 to 60% of cases (Robinson, 1943; Hughes, 1948; Ross and Herdan, 1951). In others the proportion of unexplained failures is much lower, mainly because "insufficiency of lactation" is suggested as the cause in many cases. For example, Dummer (1949) attributed 51% of failures to "physiological insufficiency," but made the observation that the term "covers a multitude of unsatisfactory causes"; Stocks and Stang (1953) considered that more than 60% of their cases were due to total failure or insufficiency of lactation; and Williams (1947) concluded that the "milk went away on resuming house-work" in 29%. Others have recorded such vague or remote causes as "psychological reasons," "worry," "excitement," "illness in the family," and "overcrowding." Most clinicians would probably agree that the causes of failure are in fact often vague and multiple.

Since women are well aware that medical opinion in general favours breast-feeding and, by implication at least, disapproves of bottle-feeding, the reasons they offer for giving it up may well be coloured by that knowledge. Even the mother who is not intent on self-justification may find it impossible to give a complete and objective account of the events which led up to her decision. Spence *et al.* (1954) say that failure of breast-feeding is "an exceedingly complex problem, difficult to approach without prejudgment, and almost impossible to assess by objective experiment." To avoid some of the faults of earlier studies, particularly retrospective inquiries, Williams (1947) suggested that a more intimate approach would be necessary. This paper describes the methods and summarizes the findings in an "intimate" study of primiparae who left hospital breast-feeding, and were followed up for three months after delivery.

Material and Methods

Sample of Women.—Between October 1, 1954, and December 31, 1955, 1,075 married primiparae, booked hospital patients resident in the City of Aberdeen, were delivered of a single healthy baby weighing 5½ lb. (2.5 kg.) or more. Of these, every ninth in order of confinement was asked while still in hospital to take part in a follow-up study. Of 119 so singled out, three refused to co-operate, 11 whose dates of discharge from hospital coincided with holidays were "lost," and 18 abandoned breast-feeding in hospital, leaving 87 to be visited at home. A random sample of this size is likely to contain very few women of the highest and lowest social classes. Since these classes show the greatest contrast in breast-feeding performance, eight women previously in professional or technical occupations and 11 who had been fishworkers were added to the random group to give a total of 106 mothers to be studied to the end of the third month.

Home Visits

The investigator (J. C. Y.) had examined daily during their stay in hospital all the prospective members of the study group and had come to know them well. The first home visit was made within two days of discharge from hospital. From experience gained in a pilot study it was decided that visits should be made twice weekly during the first month, once weekly during the second month, and fortnightly during the third month. If difficulties arose visits were made more often. Home visits were made as informal as possible and usually lasted about half an hour; they had to be limited to those times when the baby could be examined and weighed without disturbing its normal times of sleep, and when the mother was at home and not resting. On account of these restrictions only two *new* cases could be taken on each week.

The conditions for such an inquiry enunciated by Hytten and Thomson (1955) were observed: "The investigator, preferably a doctor, must be readily accepted into the patient's home and must be able to discuss the baby's feeding dispassionately and at frequent intervals, with full knowledge of all the circumstances, domestic as well as medical, and without giving the woman the impression that he* is taking sides for or against breast-

*The success of the present inquiry might well have been less had the investigator (J. C. Y.) not been a woman, married, and of about the same age as most of the subjects.

feeding. . . . Unless they feel free of guilt in expressing a preference for bottle-feeding, the truth may be concealed."

It was vital to the experiment that the mother should not believe herself to be pursued by a champion of breast-feeding. She was therefore told that the purpose of the inquiry was to study the health and growth of normal babies, and equal interest was shown whatever the method of feeding. No treatment or advice was given except, if advice was asked for, to recommend that the mother should see her own doctor, or visit a mother and child welfare clinic.

Information Collected

At each visit questions were asked, and the answers, recorded immediately afterwards, concerned: (1) *the baby*, its general health and behaviour, crying, feeding schedule, and difficulties, if any; (2) *the mother*, her general health, appetite, and energy, and the condition of her breasts and nipples; and (3) *the background*, which was described in more narrative form to cover (*a*) housing and the amount of housework done; (*b*) the mother's general capability; (*c*) the attitude to the baby and to breast-feeding of the mother, and, if possible, of the father and other relatives or other occupants of the house and their previous experience of breast-feeding; and (*d*) the influence on the mother of outside opinion.

It is obvious that any report of difficulty with breast-feeding must be a personal assessment by the mother herself and can never be reduced to a quantitative basis. One mother may consider her baby's crying to be "normal" and scarcely worth reporting, while to another the same amount of crying indicates a menace to the baby's welfare and causes worry, loss of sleep, and fatigue. To give an objective check on the subjective assessment of health and progress of baby and mother, the baby was weighed on portable scales once a week during the first two months and twice during the third month. The mother was weighed at intervals of two weeks. This presented certain difficulties: while it was obviously desirable to be as accurate as possible, undressing for the purpose would have been resented by many women and might have harmed the friendly relationship which was so important for the success of the investigation. The mother was therefore weighed each time in her ordinary clothes, but without shoes. An allowance was made for the weight of clothes. The scales themselves, which were necessarily of the portable "bathroom" type, were adjusted before each weighing.

The difficulties recorded were those brought to the notice of the investigator by the mothers themselves at the time of occurrence. They were not necessarily followed by cessation of breast-feeding. There was no attempt to systematize the inquiry in advance, and the main groups of difficulties, shown in Table I and discussed below, emerged as the records were sorted and analysed.

Results

Of the 106 women studied in this way (87 from the random sample, 8 with an upper-class background, and 11 fishworkers), 104 experienced breast-feeding "difficulties" of one kind or another, and 74 of them gave up breast-feeding within three months. The causes are shown in Table I.

Of the entire sample only two mothers experienced no difficulty during three months of breast-feeding. Both felt well, had excellent appetites, and found breast-feeding easy and enjoyable; both babies thrived. The domestic circumstances were somewhat unusual; both lived with their mothers, had little domestic responsibility, and received considerable help with the baby. Indeed, their only regular occupation was breast-feeding. One was noted initially as preferring to breast-feed, the other as indifferent. Another four of the 32 women who continued breast-feeding for three months had only trivial difficulties. The rest persevered in spite of difficulties. In all, 23 of the babies were fully breast-fed throughout the three-months period; nine others had complementary feeds of cow's milk.

TABLE I.—*Incidence of Circumstances Which Interfered with Breast-feeding and Their Influence on Weaning in 106 Primiparae*

Circumstances Interfering with Breast-feeding	No. Affected	Weaned	
		No.	%
The difficult baby:			
Excessive crying	68	41	60
Specific illness	18	4	22
Feeding defect	5	3	60
Maternal difficulty:			
Inadequate lactation	40	28	70
Breast and nipple abnormalities	41	20	49
Ill-health	8	4	50
General fatigue	47	11	23
Menstruation	4	1	25
Other influences:			
Persuasion by third person	16	12	75
Unsatisfactory housing	3	2	60
Return to work	2	2	100

Of the 74 women who gave up breast-feeding within three months, 10 did so from choice before difficulties were experienced. The remaining 64 appeared to give up because of difficulties. In the first month 46 began bottle-feeding, all but two of them within two weeks of leaving hospital; in the second month 15, and in the third month 13.

The Difficult Baby

Excessive Crying.—Of the 106 mothers, 68 (64%) became worried because the baby cried so much, and 41 of them abandoned breast-feeding at least partly because of the crying. In 29 babies the crying appeared to be associated with underfeeding; in 34 cases there was no evidence of underfeeding (in that the babies gained weight at a rate of 5 oz. (140 g.) or more weekly—see "inadequate lactation" below) and the crying was often of the type commonly described as associated with "three months' colic." In both these groups the clinical picture was predominantly that of "hunger," and the one would often have been indistinguishable from the other without a knowledge of the weight gain of the baby. The clinical features of crying from "hunger" in babies who are gaining weight satisfactorily have been described elsewhere (Yorston and Hytten, 1957); in all cases where the change was made to bottle-feeding crying ceased dramatically and the babies became placid and contented. Such babies may have a relative hypermotility of the gut, so that the fine curd of breast milk passes rapidly through the stomach, leaving it empty soon after a meal. In the remaining five cases the cause of crying could not be diagnosed. Two of these were weaned after a day or two and crying stopped at once. In the other three, crying did not persist and did not lead to weaning.

Illness.—Eighteen babies (17%) had a specific illness severe enough to interfere with breast-feeding, but only four were weaned on that account. The illnesses were: upper respiratory infection, 9 (2 weaned); pyloric stenosis, 1 (weaned); congenital heart disease, 1 (weaned); oral thrush, 4; diarrhoea, 2; and severe conjunctivitis requiring treatment in hospital, 1.

Feeding Defect.—Five babies seemed unable to suck properly and three of them were weaned for that reason. One had been a "lazy baby" in hospital, and at the age of 3 weeks began to "fight the breast," sucking for only a minute or two and then pushing away and screaming. After one day of this the mother gave up breast-feeding. Another was given complementary bottle feeds because of a cracked nipple; when the nipple had healed the baby refused to fix, even with a nipple shield, and breast-feeding was abandoned. The third, after feeding well for 12 weeks and apparently thriving, suddenly refused to suck for more than three or four minutes; engorgement was the result and breast-feeding was stopped. The two that were not weaned had been slow to feed in hospital, but they gradually improved.

Maternal Difficulties

Inadequate Lactation.—Of the 106 babies, 40 (38%) consistently failed to gain 5 oz. (140 g.) a week (taken as a criterion of sufficiency of lactation), or required complementary feeds after repeated test-weighing earlier in the lactation had confirmed insufficiency of the breast milk. In most of these cases the evidence of the weight trend or of test-weighing was confirmed by clinical evidence such as "hungry" crying. A 24-hour milk sample was obtained for analysis on the seventh day from 85 of the 106 women in the study, so that in most cases of inadequate lactation further quantitative confirmation was available. The milk analysis data are not discussed here. The group includes the 29 underfed babies already described under "excessive crying"; 11 did not cry excessively. Three subgroups may be distinguished.

Lactation Poor from the Start (12 *Cases*).—Two babies had complementary feeds in hospital after test-weighing had confirmed inadequate lactation, and they were breast-fed, with complementary feeds, for at least three months. One mother whose baby gained, on the average, only 4 oz. (110 g.) weekly and cried incessantly, consulted her family doctor, who prescribed chloral hydrate. The crying and poor weight gain continued, the baby being wholly breast-fed throughout the three months. The remaining nine women abandoned breast-feeding within six weeks, four of them after trying complementary feeding.

Lactation Beginning Satisfactorily and Then Declining (14 *Cases*).—After an initial period of satisfactory growth and behaviour the baby appeared suddenly to be underfed. Only one mother continued to breast-feed for three months. Her baby, which had been gaining 10 oz. (285 g.) a week, suddenly gained only 3 oz. (85 g.) in one week, and seemed hungry, waking within two hours of being fed and crying until fed again. The mother noticed that her breasts were less full than normal. She had been feeling very tired, but improved in health after going on holiday, and her lactation recovered quickly. In three women there was no obvious reason for the fall in the milk yield; in each it followed soon after return from hospital. Details of the remaining 10 women are shown in Table II.

TABLE II.—*Sudden Deterioration of Lactation*

Associated Condition	No. of Cases
Maternal disability:	
Cracked nipples	2
Breast abscess	1
Influenza	1
Diminished suckling due to:	
Illness of baby	2
Complementary feeding	2
Maternal worry due to:	
Illness of baby	2

Lactation Initially Sufficient But Not Keeping Pace With the Growth of Baby (14 *Cases*).—In contrast to the pattern of weight loss in the previous group an initially satisfactory weight gain became progressively less, usually over a period of a few weeks. Nine of the babies became irritable and showed increasing signs of hunger; but the other five remained quiet and seemed contented. In 8 of the 14 cases breast-feeding was maintained until the end of the third month, in two of them with the aid of complementary feeds.

Breast and Nipple Abnormalities.—Of the total of 41 women affected by mastitis or sore nipples, 29 abandoned breast-feeding, the breast lesion being partly or wholly responsible for this in 20 cases. Fifteen breast-feeding women (14%) had mastitis, with abscess formation in four. Three of them, none with abscess, maintained breast-feeding during and after treatment. Thirty-one women (28%) had sore or cracked nipples, in four cases associated with mastitis.

Maternal Ill-health.—One woman who developed gastro-enteritis and another with tuberculous adenitis and a severe non-tuberculous chest infection continued to breast-feed for three months. One with cystitis, one with influenza, one with puerperal insanity, and one with a paralysed arm which interfered with nursing stopped breast-feeding in consequence. Two others, one with cystitis and one with a generalized allergic reaction of obscure origin, eventually gave up breast-feeding for other reasons.

General Fatigue.—Forty-seven breast-feeding mothers (44%) said that they felt constantly and excessively tired; 17 of these nevertheless continued to breast-feed for three months. In the remainder, fatigue was never the sole reason for weaning, but it was an important factor in 11 cases. General fatigue was often accompanied by backache, dizziness, headaches, and repeated minor infections, such as boils and styes. Many of the women who were excessively tired lost more than the average amount of weight during lactation and were doing an excessive amount of housework.

Menstruation.—This affected breast-feeding in four cases. In three of these the milk supply diminished temporarily and the baby showed signs of hunger; in one, breast-feeding was discontinued. In the fourth case the baby had diarrhoea while the mother was menstruating.

Other Influences

Persuasion by a Third Person to Stop Breast-feeding.—Sixteen women, each of whom had experienced one or more of the difficulties listed above, came under strong professional or lay persuasion (in some cases this amounted to "nagging") to give up breast-feeding and 12 complied. Of the remaining four, two were advised by their family doctor to give up breast-feeding when mastitis occurred, but refused to do so; one was unimpressed by her dentist's statement that breast-feeding would harm her already badly carious teeth; and one did not heed a mother who thought breast-feeding was causing her to be excessively tired.

Unsatisfactory Housing.—Three women attributed difficulty over breast-feeding to unsatisfactory housing. One was given notice to quit her rooms when the baby was 6 weeks old; but, although this caused much worry, lactation was not affected. Two others, each living in a single room, found the baby's crying intolerable, and gave up breast-feeding; both suggested that the crying might have been tolerable if housing had been better, but in each case there seemed to be other more important reasons for giving up breast-feeding.

Return to Work.—Two women said from the beginning they would give up breast-feeding because they intended to return to work; neither was keen to breast-feed, though only one showed a clear preference for bottle-feeding. Five more mothers went to work before the end of the third month, all after giving up breast-feeding, apparently for other reasons. None had been keen to maintain breast-feeding.

Examples of Breast-feeding under Difficulties

Occasionally a mother would persevere with breast-feeding despite most discouraging circumstances. The following histories are illustrative.

A 24-year-old healthy woman left hospital fully breast-feeding after a trouble-free first week. She was quite keen to breast-feed—largely, it seemed, because her own mother was particularly enthusiastic about it. The baby was well and contented during the first month, apart from conjunctivitis. At about 4½ weeks he began to cry for long periods in the evening and "seemed hungry": the crying was of the colicky type and was only temporarily relieved by feeding. It continued with varying degrees of severity during the remainder of the survey period. The mother felt particularly tired after leaving hospital and needed rest for much of the day. At 6 weeks she developed mastitis and wished to give up breast-feeding, but her doctor and her mother persuaded her to carry on. The mastitis cleared up, but she became progressively more fatigued. At 8 weeks the baby was given complementary feeds of cow's milk to try to stop the crying, and at 12 weeks cereals were introduced, but four-hourly breast-feeding was still continued at 14 weeks.

A woman aged 20 had cracked nipples and at the time of leaving hospital one nipple was not fully healed. The other nipple cracked again at home and it was three weeks before both were healed. The baby had mild conjunctivitis during the first week at home and at about 3 weeks developed a cold which persisted during the rest of the three months. On two occasions there were acute exacerbations with coughing and vomiting. Apart from this the baby cried infrequently and gained weight well. At 3½ weeks the mother developed swollen neck glands which proved to be tuberculous, and these were curetted at the surgical out-patients' department at 12 weeks. At 5½ weeks she

had to go to bed because of acute bronchitis with pleurisy. At this point her husband tried to persuade her to abandon breast-feeding, but she was anxious to continue and was supported by her doctor. She was still fully breast-feeding at three months.

Breast-feeding in hospital was uneventful in another woman, aged 24, and she had an abundant milk supply. The baby developed thush infection of the mouth during the second week, and several times during the first 3 months had an infection of the upper respiratory tract. From the third to the sixth week he cried a great deal in the evenings; the crying was "colicky" in type and was not relieved by breast-feeding. The mother had severe "colds" at 6 and 9 weeks respectively and complained of excessive tiredness. At 11 weeks she thought her milk supply was diminishing; the baby demanded feeds at three-hourly intervals and woke at 2 a.m. Mixed feeding was introduced and the baby became more contented. At 12 weeks the left nipple cracked. The mother was still giving breast-feeds four-hourly at the end of three months.

Summary of the Influence of Breast-feeding Difficulties

Where several difficulties occur simultaneously, as often happens, it is not easy to assess the relative importance of each in causing failure of breast-feeding. No attempt has been made in this investigation to determine a primary cause of failure in each case. Table I gives the total numbers of women affected by each "difficulty" encountered and the percentage of those affected who gave up breast-feeding. The most common complaints were, in order of frequency, babies who cried excessively, maternal fatigue, abnormalities of the breast and nipple, and inadequate lactation. Excessive crying and inadequate lactation often occurred together, and most frequently resulted in weaning. Mastitis and sore nipples were followed by weaning in just under half the affected cases, but only one-quarter of the women who complained of fatigue weaned the baby. Sixteen mothers were under pressure by relatives and friends to give up breast-feeding, and 12 of them did so; in these cases another factor, usually excessive crying of the baby, was always present. All mothers who had initially expressed a strong preference for bottle-feeding gave up breast-feeding within a few weeks, even if they had experienced no difficulty.

It was evident that symptoms suggesting harm to the baby, such as crying, are more likely to result in weaning than personal difficulties or discomforts such as sore nipples or fatigue, which do not affect the baby directly.

Incidence of Breast-Feeding Difficulties Within Social Classes*

Interclass comparisons are complicated by the fact that since upper-class women breast-fed longer than women in the lowest social groups (average length eight and three weeks respectively) they had more time in which to experience difficulty.

Detailed findings are not presented. In general it appeared that women in the upper social classes experienced such difficulties as a crying baby, inadequate lactation, and general fatigue more often than women in the lower classes. The latter had more difficulty from "poor housing" and more of them expressed antagonism to breast-feeding (see "attitudes of mind" below). The social classes differed little in other respects.

Social Classification.—The Registrar-General's Social Classification (General Register Office, 1951) is not entirely suitable for female occupations. For the purposes of this inquiry, mothers' occupations before marriage were classified as follows (Illsley, 1956). (1) *Professional and Technical:* e.g., teachers, trained nurses, doctors, social workers. (2) *Clerical:* e.g., clerks, typists, telephonists. (3) *Skilled Workers:* e.g., shop assistants, machine operators, weavers, dressmakers, waitresses. (4) *Semi-skilled and Unskilled Workers:* e.g., bus conductresses, domestic servants, packers, bottlers. (5) *Fishworkers:* e.g., filleters, washers, gutters, curers. Fishworkers would ordinarily be placed among the skilled workers, but experience in Aberdeen shows that in this city they are, from the point of view of social standing, more properly ranked below the group of semi-skilled and unskilled workers.)

It therefore seems that women in the upper social classes give up breast-feeding less frequently and less early than those in the lower classes because they are less easily discouraged by difficulties experienced, not because they experience less difficulty. For example, of women affected by mastitis and sore nipples, the proportion who gave up breast-feeding rose steadily from nil in the professional and technical group to three-quarters in fishworkers.

This suggests that attitude of mind may be as important as physical disability in determining whether breast-feeding will stop or be continued in the face of difficulties.

Attitudes of Mind

It is not easy to discover a mother's real attitude to breast-feeding while she is in hospital, where she feels that she is expected to breast-feed; no attempt was made to find out until the first home visit. It would undoubtedly have been easier to get an expression of opinion at a later visit, when mother and investigator had become better acquainted, but by that time the original attitude might well have been modified or obscured by the ease or difficulty clearly experienced. What was recorded was each mother's attitude to breast-feeding just after leaving hospital.

Attitudes to breast-feeding at the time of the first visit were classified as follows. (A) *Unqualified enthusiasm:* "I always thought I would breast-feed"; "I definitely want to breast-feed." (B) *Preference:* "I want to breast-feed if I have enough milk"; "I'd like to try to breast-feed; it's supposed to be best, isn't it?" (C) *Indifference:* "I will try it, but will be quite happy to change to the bottle if necessary"; "I'll try to breast-feed so long as everything is all right." (D) *Antagonism:* "I want to bottle-feed"; "I don't want to breast-feed, but my husband has persuaded me to do it for a while."

The incidence of attitudes, so defined, is closely related to social class. Table III shows that in the professional classes about one-third had an A attitude and none were in group D. Among fishworkers none had an A and almost half had a D attitude. Also shown are the numbers who breast-fed for at least three months in each social class and attitude group. It is clear that attitude is more important than social class in determining whether breast-feeding will be maintained or not. A strong initial preference for breast-feeding gives a good chance of success whatever the social class.

TABLE III.—*Number of Women in Each Attitude Group Within Social Classes*

Attitude	Social Status: Professional and Technical	Clerical	Skilled Manual	Semi and Unskilled Manual	Fishworkers	All Social Classes
A	5 (4)	2 (2)	4 (1)			11 (7)
B	8 (3)	14 (7)	17 (8)	11 (3)	3 (1)	53 (22)
C	3	7	14 (3)	4	4	32 (3)
D			1	3	6	10
All Attitudes	16 (7)	23 (9)	36 (12)	18 (3)	13 (1)	106 (32)

Numbers in parentheses represent those who breast-fed for at least three months.

TABLE IV.—*Proportion of Women in Each Attitude Group Who Abandoned Breast-feeding in Association with Certain of the More Common Difficulties Experienced. Figures in Parentheses are the Numbers From Which Percentages are Derived*

Cause of Breast-feeding Difficulty	Attitude: A	B	C
Baby crying	25% (8)	50% (38)	87% (22)
Inadequate lactation	29% (7)	70% (20)	93% (13)
Breasts and nipples	20% (5)	41% (22)	77% (13)
General fatigue	0 (6)	8% (24)	53% (17)
Persuasion to stop breast-feeding	50% (4)	75% (8)	100% (4)

Table IV shows how attitudes and persistence with breast-feeding were related. It shows that the proportion of

mothers who wean on account of any particular difficulty is closely related to attitude. That does not mean that even an A attitude ensures adequate lactation. Of women with an A attitude whose babies cried excessively, only 25% gave up breast-feeding compared with 50% in group B and 87% in group C. But half the mothers in group A who were still breast-feeding at 3 months were giving complementary feeds, and of seven whose babies failed to gain 5 oz. (140 g.) weekly five were still breast-feeding at 3 months. Two of the babies cried constantly as well as giving evidence of underfeeding by their failure to gain weight satisfactorily, and two had complementary feeds throughout. By contrast, of 13 mothers who had no preference for breast-feeding (C attitude) and whose babies showed similar evidence of underfeeding, only one continued to breast-feed for three months. It seems reasonable to suppose that if bottle-feeding is necessary it is simpler to go over to it entirely than to maintain part breast-feeding and part bottle-feeding, and the higher proportion of dual feeding in the upper social groups must be the result of either a firm conviction that there is special virtue in breast-feeding or a superior determination to ignore its difficulties.

Breast-feeding Compared with Bottle-feeding

Of 46 women who gave up breast-feeding within the first month, 38 were successfully followed up until the end of the third month. Of the remaining eight, one was admitted to a mental hospital at two weeks, one baby was admitted to hospital because of a congenital cardiac defect; one family left Aberdeen at 8 weeks; the other five mothers returned to work and it proved difficult to trace the babies, since they were left with relatives all day.

Of the 38 mothers who continued in the study, six had given up breast-feeding for no other reason than that they preferred bottle-feeding, and the others because of one or more of the difficulties already described. These 38 mothers will be considered as a group and compared with 32 mothers who continued to breast-feed throughout the second and third months.

The findings are summarized in Table V. It is quite clear that both mothers and babies did better with bottle-feeding. The babies cried less, put on more weight, and were at least as healthy; and the mothers, apart from escaping trouble with breasts and nipples, were less tired. While it might be argued that these figures are too small for generalization, a much larger investigation now in progress suggests that this picture fairly represents the general position in Aberdeen.

TABLE V.—*Comparison of Difficulties Experienced During the Second and Third Months by* 38 *Mothers Who Had Abandoned Breast-feeding and* 32 *Who Continued to Breast-feed*

Difficulty	38 Bottle-feeding	32 Breast-feeding
Excessive crying	8	17
Illness of baby	11	9
Underfeeding	5	13
Breast and nipple abnormalities	1	7
Maternal ill-health	2	2
Maternal fatigue	10	16
Menstruation affecting infant feeding	—	2
Housing difficulty	—	1
Mother well	25	8
Baby thriving	22	10
Mother well and baby thriving	20	6

Discussion

For a primipara without domestic help normal breast-feeding is exacting, especially during the first weeks after confinement. Her main concern is for the baby's welfare, and she is likely to spend six to eight hours daily feeding, changing, and washing it and generally catering for its needs; and at the same time she has to run her home and prepare meals as usual. She is often emotionally unstable and often lacks confidence in her ability to manage the baby; molehills may appear as mountains. The physical strain is increased by the fact that she cannot count on more than about four consecutive hours' sleep. To produce the increasing amounts of breast milk needed for the growing baby she has to drink and eat more than usual; otherwise she must lose weight excessively, or the flow of breast milk must diminish.

It may be thought that this investigation overestimates the difficulties of breast-feeding in general because it is concerned with first lactations only, but the success or failure of the first may well determine whether a second will be attempted, and in subsequent lactations the domestic load is increased by the previous children.

According to Isbister (1954), "The happiness and exhilaration associated with relaxation and relief of tension that accompany a normal breast-feed is the right of every mother and of great importance to the woman in the puerperium." Illingworth (1953) says: "I have not found papers which show that there are any disadvantages in breast-feeding. . . . Breast-feeding is easier and cheaper for the mother. It may have advantages from the psychological point of view. There are no disadvantages of importance."

Mothers do not seem to agree with such pronouncements. After studying breast-feeding in Aberdeen for several years, we have been forced to recognize that remarkably few mothers say that breast-feeding was easy and satisfactory and even fewer that it induced "happiness and exhilaration." Again, most mothers who have given up breast-feeding are emphatic that when the baby was given bottle-feeds he slept better, cried less, required less attention, and was generally healthier, and that they themselves felt less tired and harassed and more confident. There is, in fact, a widespread preference for bottle-feeding, particularly among working-class mothers, who are prepared to justify their preference with a wealth of personal experience to any friendly listener. A majority of mothers act on this preference by giving up breast-feeding, although they are aware that most doctors, nurses, and health visitors disapprove.

It is important for the medical and nursing professions to decide whether this remarkably consistent testimony by mothers, that breast-feeding is seldom an unqualified success and that bottle-feeding gives less trouble on the whole, should be accepted or refuted. If we wish to halt or reverse the present decline in breast-feeding new methods will have to be adopted. But we must first ask ourselves this question: If medical education were more successful in inculcating maternal attitudes favourable to breast-feeding, would most mothers then find breast-feeding as easy, beneficial, and even pleasurable as has been claimed? The present study was undertaken to try to answer such a question. We wished to know if an observer, present when the events were taking place, would find that breast-feeding was generally easier than the mother claimed, and if it was given up in favour of bottle-feeding out of prejudice.

It is clear that the mother's attitude plays a considerable part. Nevertheless, relatively few mothers were obviously prejudiced against breast-feeding from the start, though many were only lukewarm in its favour. It was shown that the maternal attitude accounts for most of the social-class gradient in breast-feeding rates, a favourable attitude being more common in the upper social classes and less common at lower social levels.

It is not surprising that attitude should be more closely related to breast-feeding performance than social class; the former is specifically concerned with breast-feeding, the latter is not. At no social level, in a community such as our own, is there a strong spontaneous folklore which makes breast-feeding the obvious and "natural" thing to do. Breast-feeding in public would be considered indecorous, perhaps even indecent. Medical propaganda in favour of breast-feeding scarcely affects children, who, by contrast, are aware from an early age of the impressive pictures of bonny babies assiduously advertised by manufacturers of breast-milk substitutes.

In the present study only 32 out of 106 primigravidae maintained breast-feeding till the end of the third month. Only two of these found breast-feeding to be an unqualified success; although neither had started with a strong preference for breast-feeding, in both the domestic circumstances were unusually favourable. Of the remaining 30, a few escaped with only minor trouble. The majority found breast-feeding to be difficult and worrying, and none of them found it physically or emotionally pleasurable. Half of them felt very tired, and many were seriously worried because the baby cried a great deal or became ill. We obtained evidence supporting an earlier conclusion "that about one-third of primigravidae have an inadequate capacity for lactation because of either a poor milk yield or a low fat content, or both" (Hytten, 1954a).

By contrast, 20 of the 38 mothers who gave up breast-feeding within a week or two of leaving hospital remained very well and had no anxiety about the baby. Six of them had stopped breast-feeding because they openly preferred bottle-feeding; the remainder because of some real or suspected difficulty. Out of the total of 38, 25 mothers and 22 babies did well. Only eight of these mothers complained of chronic fatigue and two others of slight or transient fatigue.

In modern society, the women who make the greatest effort to carry on breast-feeding after leaving hospital come mostly from the upper social classes, despite the fact that in some ways they have more difficulties to contend with than those from the lower classes. They are older, on the average, and are less likely to produce an initially satisfactory flow of breast milk (Hytten, 1954b, 1954c). They set themselves high standards of housewifery and child care, and worry more about minor deviations from what they consider normal. Their social circumstances may also involve the expenditure of more physical energy, particularly in these days when domestic help is both scarce and expensive.

Women in the lower social classes, being younger and having less exacting responsibilities, are in many ways at an advantage if they decide to breast-feed, but relatively few are convinced that it has any advantage to outweigh the reassuring fact that with a bottle "you can see what the baby is getting." The results of this inquiry lend them support, and, since the weaning rates in Aberdeen are similar to those reported from other parts of Britain, it is probable that a majority of mothers in other areas hold similar views.

It seems likely, then, that many of the difficulties of breast-feeding in modern society result directly from the pressure of civilization. The customs of primitive society may be more conducive to successful breast-feeding. In many tribes the mother does little else but care for her baby, at least for some weeks after parturition, since under the "joint family" system she is relieved of routine domestic responsibility and puts the baby to the breast whenever it seems hungry. The fact, too, that she knows of no other way to feed a young baby may prevent any doubt arising in her mind about her ability to breast-feed, and should save her from the danger of too much and conflicting advice. Her hopes for the individual baby will doubtless be less exacting, since the birth and the infant mortality rates are both relatively very high. We do not know how efficiently the babies are nourished compared with our standards.

A woman who is determined to breast-feed may persist even when the chances of success are small, and when a change to bottle-feeding would benefit both mother and child. This is well illustrated by the history of a former nurse who was obsessed with the importance of continuing to breast-feed, although the baby was crying incessantly and gaining only 4 oz. (110 g.) a week. She was convinced that the crying was due to colic, which she attempted, without much success, to subdue by the administration of chloral hydrate; she continued full breast-feeding for three months. It is quite possible that a baby reared in this way may be damaged both physically and psychologically, and the mother subjected to much pointless and avoidable strain. Where breast-feeding policies are pursued too enthusiastically, such cases may not be very unusual, and a high rate of "success" in breast-feeding may conceal a good deal of ill-health.

Since the mother's attitude is an important influence on the outcome of lactation, it is reasonable to assume that breast-feeding rates could be raised by intensive propaganda. The justification in more fundamental terms for such propaganda is, however, doubtful. While many more women might be persuaded to make the effort to maintain breast-feeding, the fact remains that, even among women in the upper social classes who are keen to breast-feed, only about half do so for three months. An appeal to safety is not nowadays wholly convincing, since infant mortality has continued to fall *pari passu* with the decline in breast-feeding.

The moral seems clear. We should help in every way possible the woman who wishes to breast-feed, but we are not justified in putting pressure on those who are unwilling or who appear to be unable to breast-feed efficiently.

Summary

An intensive follow-up for three months was made of 106 primiparae who left Aberdeen Maternity Hospital breast-feeding. All but two of them experienced difficulty with breast-feeding and 74 abandoned it within three months. More than one difficulty often occurred simultaneously, and the relative importance of each was usually impossible to assess. The most common complaints were of babies who cried excessively, maternal fatigue, breast and nipple complications, and inadequate lactation. Symptoms suggesting harm to the baby, such as crying, were more likely to result in weaning than difficulties or discomforts affecting the mother only.

The most important influence in determining whether or not breast-feeding was abandoned in the face of difficulty was the mother's attitude of mind on which social-class differences in performance seemed mainly to depend.

Mothers who continued to lactate throughout the three months were more often unwell and worried than those who abandoned breast-feeding soon after leaving hospital, and the breast-fed baby had no obvious advantage.

It seems that the breast-feeding mother in modern urban society often has to accept a heavy load of discomfort and disability, and that this is attributable more to her way of life than to the fact of breast-feeding *per se*.

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LARGE EPIDEMIC OUTBREAK OF VOMITING ASSOCIATED WITH MENINGISM AND EXANTHEM

CLINICAL AND EPIDEMIOLOGICAL OBSERVATIONS

BY

I. ASH, M.D., D.P.H.

Medical Officer of Health, Epping and Harlow Urban and Epping and Ongar Rural District Councils

Early in October, 1956, the headmistress of an infants' school in Harlow, Essex, informed the Public Health Department of a sudden outbreak of vomiting and diarrhoea amongst her pupils. At first it was thought to be food-poisoning, but preliminary investigations did not confirm this diagnosis, especially as at the same time it was learned from one of the general practitioners that during the past fortnight he had seen a number of patients complaining of vomiting, severe headache, neck rigidity, and occasional diarrhoea. Other general practitioners were contacted and most of them confirmed the occurrence of similar cases. Notifications had also started coming in of non-paralytic poliomyelitis, but, although the clinical symptoms and C.S.F. findings seemed to corroborate the diagnosis, it was obvious from epidemiological observations that the disease was not poliomyelitis. It soon became apparent that there was in Harlow a sharp epidemic outbreak of an obscure infection believed to be caused by a virus.

It is difficult to estimate the extent of the epidemic because most of the cases were very mild, the patients recovering within 24 to 48 hours, without coming to the attention of either their family doctor or the Public Health Department. However, from the available information it can be deduced that there were several hundred cases in the town, over 170 of which were reported by the schools. Fourteen patients were admitted to hospital.

Clinical Features

In the mild cases vomiting was the most prominent symptom. The usual history was that of a child suddenly being sick at school or waking up at night or in the early hours of the morning and vomiting in bed. In adults such vomiting was usually less precipitous and was accompanied by headache. In some patients there was a short prodromal period of general malaise. The following are two fairly typical cases.

Case 1.—A boy aged 4 years. October 16: Suddenly woke up during the night and was sick in bed. Continued vomiting until late the next morning and complained of headache. Slight diarrhoea. Temperature 100° F. (37.8° C.). In the afternoon very listless but otherwise feeling all right. Completely recovered next day.

Case 2.—A male teacher aged 34. October 15: Woke up at 6 a.m. feeling intense nausea and frontal headache followed by repeated vomiting. Later in the morning went to work but returned home after two hours complaining of headache, shivering, thirst, and prostration. Temperature not taken. For a further two days was off colour and then returned to normal health.

Many patients presented a more complex clinical symptomatology, often with meningism and sometimes with exanthem. Over 80 non-hospital cases were investigated, but, as this is a relatively small proportion of the total number and because many cases were selected for investigation on account of their clinical interest, a detailed analysis of them tabulated according to age, sex, presence or severity of certain symptoms, etc., would only give a biased and misleading picture of the whole epidemic. Therefore the following is simply a description of the main symptoms in their approximate order of frequency.

(1) *Nausea and/or Vomiting:* vomiting was projectile and sudden and consisted of bilious fluid with mucus; nausea at times preceded or replaced vomiting. (2) *Headache:* this was usually very severe and mainly post-orbital; less frequently it was occipital, particularly when associated with neck rigidity. (3) *Anorexia.* (4) *Upper respiratory symptoms:* injection of fauces was a very common finding, though only some patients actually complained of sore throat; a few had a cough. (5) *Pyrexia:* usually moderate, rarely reaching 103° F. (39.4° C.) and falling by lysis. (6) *Generalized aches and pains.* (7) *Sweating:* mainly at night and very profuse. (8) *Drowsiness.* (9) *Prostration.* (10) *Neck and back rigidity* in many cases was very pronounced and a positive Kernig's sign could often be elicited. (11) *Giddiness:* often pronounced in the more severe cases. (12) *Photophobia:* many patients also complained of pain on moving their eyes; diplopia in two cases. (13) *Abdominal pain:* more often complained of during the later stages of the epidemic, when it became very severe. (14) *Muscular tenderness* seldom associated with transient weakness of a group of muscles. (15) *Diarrhoea:* only mild and of short duration and not a common feature. (16) *Enlargement of lymph nodes:* the tonsillar and occipital glands were mostly involved. (17) *Exanthem* was observed in only 13 cases and was unrelated to the severity of the other symptoms. In fact, in some of the multiple cases occurring in families it was the only pathological symptom. The rash was usually rubella-like but of a deeper colour and more punctate, sometimes petechial. It affected the trunk, thighs, and face. The duration of the exanthem was on an average three to four days, but in one case it had appeared and disappeared within an hour. (18) *Otalgia* in a few cases. (19) *Retention of urine:* transient and in only two cases.

In cases with meningeal involvement the onset was less sudden than in those without. Complaints of anorexia, general malaise, headache, aches and pains, and sore throat preceded by several days the acute phase of the disease. In many cases the symptoms subsided on the second or third day of the illness, only to reappear with increased severity and meningism within 24 to 36 hours. The duration of the more severe cases was on an average five to eight days, and recovery was complete though lassitude persisted somewhat longer.

Case 3.—Housewife aged 37 years. October 16: Complained of general malaise and lassitude which with vague aches and pains in the back continued for two days. On the third day felt well but later in evening developed very severe headache which kept her awake at night. Temperature normal. During next four days the headache became worse and she complained of giddiness, photophobia, vomiting, and profuse sweating. Temperature around 100° F. (37.8° C.). Pronounced neck and back stiffness with positive Kernig's sign. All these symptoms completely disappeared on eighth day, leaving behind considerable prostration which lasted for a further three days.

Family Outbreak

In family outbreaks the variety and severity of symptoms differed from case to case.

Case 4.—Infant girl aged 10 months. September 4: Very restless in morning—later developed a fine punctate rash all over body. Showed signs of discomfort for another day and then completely recovered. Rash vanished four days after its appearance.

Case 5.—Sister of Case 4 aged 3½ years. September 6: Complained of abdominal pain and generalized aches. During the following day was very drowsy and in the evening developed a rash on her thighs and abdomen. During next four days all symptoms gradually cleared up and she recovered.

Case 6.—Brother of Cases 4 and 5 aged 2½ years. September 7: Woke up at night with abdominal pain. Next day complained of general malaise, drowsiness, and slight diarrhoea. A rubella-like rash appeared on the body. Gradual complete recovery in course of next three days.

Case 7.—Mother of Cases 4–6 aged 23. September 9: Woke up with a headache which got progressively worse. Next day felt very ill—complained of drowsiness, photophobia, headache, and stiffness of the neck. These symptoms gradually subsided during next few days and she made a complete recovery.

Case 8.—Salesman aged 24 (husband of Case 7 and father of Cases 4–6). September 9: In the evening felt cold and shivery. Next day had severe headache in occipital region with pain radiating down the neck, generalized aches and pains in whole body, sore throat, drowsiness, temperature 102° F. (38.9° C.). During the following day felt well except for residual slight headache. The day after again complained of severe headache, profuse sweating, and pyrexia with pain in the neck and sore throat. Vomited several times and was troubled by stiffness of neck and back. A slight rash appeared on face. Admitted to hospital on September 13. Temperature 101.8° F. (38.8° C.), pulse 110, respirations 28. Erythema of face, neck, and front of trunk. A coated tongue, injected throat, and neck and back rigidity. All reflexes present and equal. No other abnormal signs. Blood: Hb, 96%; white cells, 7,100/c.mm. (polymorphs 68%, lymphocytes 26%, monocytes 5%, eosinophils 1%); E.S.R., 7 mm. (Westergren). C.S.F.: protein, 40 mg./100 ml.; globulin, negative; chlorides, 720 mg./100 ml.; glucose normal; cells, 27/c.mm.; stained film small lymphocytes only. Throat swab: moderate growth of *Streptococcus viridans* and *Neisseria catarrhalis*. Stools: tissue culture negative. The pyrexia settled after 36 hours but there was a frequency of micturition due to a urinary infection with *Escherichia coli*. This condition cleared up in five days with sulphonamide treatment. Complete recovery.

Cases 4–7 were not seen by a doctor and their histories were obtained only after recovery and subsequent to the hospital admission of Case 8.

There were other similar family outbreaks in which some cases had pronounced meningeal symptoms and were admitted to hospital; others suffered from vomiting and headache only, or from an exanthem without any other pathological symptoms.

In the 14 hospital cases the symptoms were distributed as follows: pyrexia 14 cases, neck rigidity 11 (positive Kernig sign in 7), severe headache 10, congested fauces 10, nausea and vomiting 8, pains in limbs 5, drowsiness 5, abdominal pain 4, exanthem 3, profuse sweating 2, vertigo 2, photophobia 2, enlarged lymph nodes 2, otalgia 2, diarrhoea 1, diplopia 1.

Laboratory Findings

Blood.—Specimens from 17 patients were examined. Haemoglobin, white-cell count, and E.S.R. were mostly within normal limits. The differential count showed relative lymphocytosis of up to 54%, with an increase of monocytes up to 12% and a slight increase in eosinophils. There were no abnormal lymphocytes characteristic of glandular fever. Paired serum specimens of six patients were sent to the Central Public Health Laboratory, Colindale, where tests for mumps, lymphocytic choriomeningitis, influenza A and B, A.P.C. group, Q fever, psittacosis, *Streptococcus M.G.*, *Leptospira icterohaemorrhagiae*, and *L. canicola* were negative.

Cerebrospinal Fluid.—In only nine hospital cases were lumbar punctures done. The C.S.F. was sterile on culture and the only changes were occasionally increased protein (up to 140 mg./100 ml.) and pleocytosis with a cell count varying from 27 to 2,500/c.mm. In two of the cases the cells were at first mainly polymorphs (86% and 90%) but in subsequent specimens lymphocytes predominated in a similar proportion. In each of the other seven cases only one lumbar puncture was performed and the differential cell count showed lymphocytosis of between 75% and 100% in all but one of them. In the latter there were 75% polymorphs and 25% lymphocytes.

Faeces.—Bacterial cultures of 40 cases were negative for organisms of the salmonella and shigella groups. Virus investigations were carried out at the Central Public Health Laboratory, Colindale. One batch of 22 specimens came from children from the infants' school which had first reported an outbreak of vomiting. Rectal swabs of some close family contacts were also included. A cytopathogenic agent was isolated in three cultures. In two cases it was identified as Coxsackie B_1 and was grown from the stools of a 5-year-old girl and her father, both of whom had suffered only from sudden vomiting with headache lasting 24 hours. The virus isolated in a third case, also from a girl of 5 with similar symptoms, could not be identified despite repeated attempts. However, it was not poliomyelitis virus and did not appear to fall within the Coxsackie B, Coxsackie A9, or ECHO group of viruses. Subsequently, when the epidemic had spread and cases with meningeal involvement and rashes had appeared, the laboratory, owing to pressure of work, could accept only four specimens of such cases and all were negative on tissue cultures.

Nose and Throat Swabs.—In only two cases was there a growth of *Str. viridans*. Four other bacterial cultures were negative.

Epidemiology

The earliest known case in the described outbreak occurred in May and was diagnosed at the hospital as lymphocytic choriomeningitis, presumably on the grounds of a predominantly lymphocytic pleocytosis in the C.S.F. No virus investigations or neutralization or complement-fixation tests against lymphocytic choriomeningitis were carried out. Between May and the last week in September only two more cases were admitted to hospital, one diagnosed as mild encephalitis, the other as non-paralytic poliomyelitis. Both were adults in their twenties. There is no indication that the minor form of the disease was widespread during that period.

On September 18 a 5-year-old girl attending a local infants' school was taken ill with severe headache, vomiting, pyrexia, drowsiness, and, later, neck and back stiffness. She was admitted to hospital on September 21 as a case of meningitis. Two days after this girl's first day of absence from school other children in the same classroom started having bouts of sudden vomiting, sometimes associated with mild diarrhoea and abdominal pain or with headache. The infection rapidly spread to other classrooms and to the adjoining junior school and later to practically all the schools in the town. A number of teaching and non-teaching staff were also affected. The epidemic reached its peak in October, when not only the total incidence was high but the proportion of patients with meningeal involvement was considerable. Only relatively few cases, however, were admitted to hospital, because by then all general practitioners in the area knew of the outbreak and of its clinical features and were therefore less alarmed by symptoms which at times suggested poliomyelitis.

In November and December there were only isolated cases with meningeal involvement, although the number of abortive cases was still quite high. At that time it was also noticed that besides vomiting severe abdominal pain of a myalgic type had become a prominent feature. By early January, 1957, the epidemic had spent itself.

The disease mainly affected children and young adults of either sex, meningism being both more frequent and more severe in the latter. Infectivity was very high and multiple cases in families were common. The incubation period was around two days. This could be deduced from the fact that when the infection was first introduced into a family or a school subsequent cases appeared at an interval of one to three days. It was also established in three cases that the first symptoms developed two days after a known and only contact with an infected person.

It is interesting to note that in those schools which rigorously enforced the exclusion for a week of all children who had suffered from sudden unaccountable vomiting the incidence of the disease decreased very considerably. A transient drop in the number of children affected was also observed in all schools for a short time after the mid-term break at the end of October.

The frequent finding of injected fauces points to an upper respiratory portal of entry of the infection.

During the first weeks of the epidemic there were no other infectious diseases in the area except a few sporadic cases of whooping-cough and measles. In the third week of October, however, the incidence of measles increased sharply and continued to do so with fluctuations until it reached a peak of 273 cases during the week ending January 5, 1957.

Discussion

Most of the Harlow cases were mild and in many ways resembled "epidemic nausea and vomiting" ("winter vomiting disease"). The common features were very short incubation period, precipitate vomiting, abdominal pain, anorexia, headache, injected fauces, and occasional diarrhoea. This disease has been known as a definite syndrome since its first description by Zahorsky (1929) in the U.S.A. In this country outbreaks have been reported by various authors, including Bradley (1943), who made an extensive study of the disease. The causative agent of epidemic nausea and vomiting is believed to be a virus, but it has not yet been isolated. Neither meningism nor exanthems have ever been directly associated with the disease, though Haworth *et al.* (1956) have described as "winter vomiting disease with meningeal involvement" cases in which there were changes in the C.S.F. but not physical signs of meningitis.

The more severe of the Harlow cases had the appearance of non-paralytic poliomyelitis because of their diphasic character, the C.S.F. findings, and other clinical features. However, the very short incubation period and high infectivity, the frequency of multiple cases in households, the absence of paralytic disease (except in one doubtful case mentioned below), and the failure to recover poliomyelitis virus in tissue cultures speak against this diagnosis.

Aseptic meningitis simulating poliomyelitis was first described by Wallgren (1925). Since then, and particularly in recent years, poliomyelitis-like outbreaks have been reported in this and several other countries. Although they had many features in common they nevertheless differed in some important respects. One of the main differences was in the findings of the C.S.F., and a suggestion has been made (*Lancet*, 1956) to classify the syndrome according to the presence or absence of changes in the C.S.F. Pleocytosis in cases with pronounced meningism and without encephalitic signs and sequelae is found in aseptic virus meningitis. Such cases have been reported by Parry and Good (1949), Covernton and Miles (1953), Tyrrell and Snell (1956), Pickles (1956), Garnett *et al.* (1957), Rotem (1957), and others. In some outbreaks the poliomyelitis-like disease was regarded as encephalomyelitis because the C.S.F. was normal and there were muscular weaknesses and psychological disturbances, usually transient but at times of long duration (Pellew, 1951; Sigurdsson and Gudmundsson, 1956; Ramsay and O'Sullivan, 1956; Sumner, 1956; Jelinek, 1956; Galpine and Brady, 1957; and others).

Symptomatologically the distinction between meningitis and encephalitis is not always clear-cut and some cases have been described as meningo-encephalitis (Lyle, 1956; Langdale-Smith *et al.*, 1957).

In the Harlow outbreak most cases with meningeal involvement had the clinical appearance of aseptic meningitis. Pleocytosis was found in nine cases in which lumbar puncture was done. No mental changes were observed and transient muscular weakness was seen in only a few patients. In one case, however, there was slight residual paresis of the abdominal muscles. This was diagnosed at the time as paralytic poliomyelitis, but in the light of further knowledge the diagnosis is open to doubt.

Symptoms such as mouth lesions (Tyrrell and Snell, 1956) were absent from the Harlow and other outbreaks. Acute myalgia, more prominent in cases of benign encephalomyelitis than in aseptic meningitis, appeared in the later stages of the Harlow epidemic and affected the abdominal muscles.

Virus investigations have yielded varying results. Such cytopathogenic organisms as have been isolated were from cases in which the C.S.F. showed pleocytosis and which could be described as aseptic meningitis. Crawford *et al.* (1956) reported the recovery of five strains of virus from the stools of their cases. These were small babies 3 to 14 months old who presented a clinical picture of irritability, pyrexia, vomiting, diarrhoea, and a maculopapular rash but no meningism. There was pleocytosis in the C.S.F. The strains of virus were morphologically closely related to each other but distinct from poliomyelitis, Coxsackie, and other known viruses. Tyrrell and Snell (1956) isolated a virus related to Coxsackie A, and other authors found ECHO viruses or viruses akin to this group (Boissard *et al.*, 1957; Rotem, 1957).

Coxsackie B viruses have for some time been known to be associated with certain outbreaks of aseptic meningitis (Hummeler *et al.*, 1954; Wilkins *et al.*, 1955; McLeod *et al.*, 1956). Viruses of this group are, according to Rhodes (1956), rarely found in healthy persons, so that their recovery from two of the Harlow cases may be significant though inconclusive.

It appears that different groups of viruses may be responsible for outbreaks which present a similar general clinical picture but differ in some aspects from each other. Further careful investigations will no doubt throw more light on this infection.

Summary

An account is given of a large outbreak of a disease closely resembling epidemic nausea and vomiting but with a proportion of cases exhibiting meningism and other symptoms simulating non-paralytic poliomyelitis and some with an exanthem. The differences in the clinical features of this and other outbreaks simulating poliomyelitis are discussed.

I am grateful to the general practitioners of Harlow for their co-operation; to the head teachers who promptly notified me of the cases occurring in the schools; to Dr. I. M. Tuck, of St. Margaret's Hospital, Epping, for laboratory investigations; to the Central Public Health Laboratory, Colindale, for serum and virus research; to Dr. R. W. Tannahill and Dr. E. J. Dodds, of Honey Lane Hospital, Waltham Abbey, for case histories of in-patients; and to Dr. W. H. Bradley, Dr. C. G. M. Nicol, and Dr. A. T. Roden, of the Ministry of Health, for their help and advice.

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The problem of the rheumatic diseases was twofold, said Dr. W. S. C. COPEMAN, chairman of the Empire Rheumatism Council, when addressing the Royal Society of Health on January 15. The first aspect was financial, as the present state of knowledge necessitated a large expenditure on basic research, much of which had to come from voluntary sources, chief amongst which was the Empire Rheumatism Council. The second main aspect was the provision of adequate treatment centres of high standard within the present regional organization of the National Health Service. Although two university chairs in rheumatology had been established, consultant posts in this specialty were not yet recognized by the Ministry of Health.

OUTBREAK OF ASEPTIC MENINGITIS WITH EXANTHEM

BY

J. F. GALPINE, M.D., F.R.C.P.Ed., D.P.H.
T. MORRISON CLAYTON, M.D., B.Hyg., D.P.H.
J. ARDLEY, M.B., B.Sc., D.P.H.

AND

NORMAN BASTER, M.D., D.P.H.

Wallgren (1925) postulated the existence of "acute epidemic aseptic meningitis" as distinct from non-paralytic poliomyelitis. Aseptic meningitis is now regarded as a syndrome which includes non-paralytic poliomyelitis and of which the list of causal viruses is lengthening, newcomers being Coxsackie (B) virus and, more recently, ECHO virus type 6 (Karzon *et al.*, 1956). Canicola fever may produce a similar picture (Ramsay, 1955). Encephalitic manifestations may on occasion suggest the term "meningo-encephalitis" (Galpine and Macrae, 1953).

Several reports of aseptic meningitis associated with an exanthem have been made in the last few years (*Monthly Bulletin*, 1956), including one described by Crawford *et al.* (1956) from which an enteric virus was isolated. In 1955 and especially 1956 outbreaks of aseptic meningitis associated with a rash occurred in various parts of the country (*Lancet*, 1956; Garnett *et al.*, 1957; Rotem, 1957) and strains of virus related to ECHO virus type 9 were recovered from throat washings, cerebrospinal fluid, and faeces in a number of instances (Boissard *et al.*, 1957). A comparable illness has been reported on the Continent by Nihoul and Quersin-Thiry (1957), who isolated a virus typed as ECHO 9. In a similar report from Sweden (Johnsson, 1957) a virus related to ECHO 4 is mentioned in addition to ECHO 9. The following account is of an outbreak of this type in Coventry in the autumn of 1956.

Epidemiology

From July 28 to August 31, 1956, one case of paralytic poliomyelitis was notified in Coventry, compared with seven clinically resembling "non-paralytic poliomyelitis." Examinations of faeces and sera from five of the latter were subsequently reported negative for poliomyelitis, and, although lacking the rash or familial tendency shown later, it is likely that these cases belong to the outbreak of aseptic meningitis which followed.

In September 19 cases, in October 17 cases, in November 14 cases, and in December 3 cases of aseptic meningitis, some with a rash, were admitted to hospital from Coventry—a period when only four cases of paralytic poliomyelitis occurred in the city. If we exclude a case with poliomyelitis type 1 virus in the faeces and a case having close contact with a paralytic case, 51 of these cases remain to be considered. Inquiries showed that a number of family contacts were unwell but remained at home, and children in adjacent houses had illnesses but sought no medical advice. Twenty-three of the series were familial, being derived from nine families. Study of consecutive illnesses in several families suggested an incubation period of five or six days. Children preponderated, although a number of young adults were also affected (Table I). In the various age groups in all the families involved in the epidemic it was seen that 54% of the pre-school children exposed to risk, 56% of the schoolchildren, and only 17% of the adults became victims of the disease. The youngest patient was 15 months old and only two were under 2 years.

TABLE I.—*Incidence by Age and Sex*

Age	Males	Females
0–11 months	0	0
12–23	1	1
2–4 years	7	1
5–14	15	12
15–24	3	2
25–34	1	6
35	1	0
36	1	0
Total ..	29	22

The majority (42) of the cases arose in neighbouring districts in the north-east of the city. The chief concentration was in a modern housing estate where 12 families were affected, and a group of houses surrounding a grassy area about the size of a village green provided 14 cases between September 17 and 23 with up to four cases from the same house. A near-by stagnant pool—a favourite spot for the local children—was blamed by several parents for the spread of the infection. Just before this time the persistently dull wet weather had relented to give a short Indian summer with a maximum shade temperature on September 13 of 75.8° F. (24.3° C.) and over 70° F. (21.1° C.) on September 22 to 25. Nine cases of aseptic meningitis occurred in areas of Coventry remote from the main focus, a direct link with the latter being established in three cases. It is remarkable that these scattered cases did not give rise to any known secondary foci.

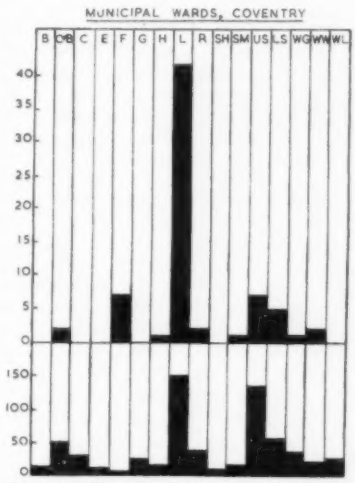

FIG. 1.—Showing incidence of aseptic meningitis (above) and of Sonne dysentery (below) from September to December, 1956.

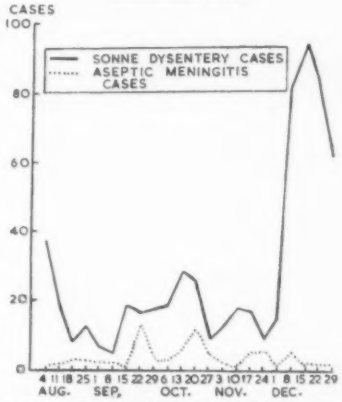

FIG. 2.—Showing the curves of incidence.

The main incidence of aseptic meningitis followed quickly on the start of school term in early September and was accompanied by an increase in Sonne dysentery centred in the same area (Fig. 1), the two curves of incidence following closely for time and place (Fig. 2). Eleven of the 12 families mentioned above had a child attending the same school. The absence rate at this school was about 10%, approximately double that of the current average for all local authority schools in Coventry, presumably owing to the combined influence of Sonne dysentery and aseptic meningitis. In the nine families having more than one member in hospital a school child was clearly the first household case three times, a pre-school child once, an adult once, and in the remainder members fell ill approximately simultaneously.

It is interesting that 73% of the cases of aseptic meningitis and 46% of all Sonne dysentery in the city in the last quarter of 1956 arose in a part of the city where housing standards are high, the estates being of comparatively recent development and the schools equally satisfactory. Following the onset of colder weather in early December the incidence of meningitis declined but Sonne dysentery showed a sharp increase, due mainly to an outbreak in another school in the area.

TABLE II.—*Symptoms and Signs in 51 Cases*

Pyrexia	49	Cough	6
Headache	51	Nasal discharge	4
Vomiting	41	Limb pains (usually legs)	8
Neck and/or back rigidity	37	Abdominal pain	4
Kernig's sign	18	Photophobia	9
Rash	19	Drowsiness	2
Backache and general aches	16	Delirium	1
Mild sore throat (no exudate)	13	Diarrhoea	1

Clinical Description of 51 Cases (Table II)

In at least 18 cases (admitted in the first and second day of the disease) there was early onset of meningeal symptoms. Another 19 cases were admitted in their third and fourth day and 14 cases on the fifth day or later. In four of the latter the history suggested a distinct pre-meningeal phase followed by a remission before onset of meningeal symptoms. The duration of illness (estimated from day of onset to final return of temperature to normal) varied from 2 to 13 days, but 41 cases lasted four to nine days. Pyrexia was usually considerable, and reached 101 to 103° F. (38.3 to 39.4° C.) in 35 cases, the maximum recorded being 103.8° F. (39.9° C.). In 20 cases a remission or intermission of pyrexia lasting one to three days occurred whilst in hospital, the final elevation being sometimes the higher. Fall of temperature was by rapid lysis, taking one to two days to reach normal.

The patients typically presented with headache (often severe, irritability, pyrexia, and unimpaired consciousness. Neck or back rigidity was recorded in 37 cases only, and in nine of these it was slight, as was Kernig's sign when present. In at least 20 cases, therefore, these signs were slight or absent. No nystagmus was seen. Superficial and tendon reflexes were usually brisk and plantar responses always flexor. Vomiting was common before admission but seldom gave much trouble afterwards. Limb pains sometimes caused fear of poliomyelitis, and in two cases with abdominal pain anxiety was caused in one by its severity (with vomiting) and in the other by localization in the right iliac fossa. No thoracic pains were noted.

In 12 out of 32 cases where special search was made small shotty lymphatic nodes were palpated in the posterior triangles of the neck, but they were deemed to be too small to be of special significance. Splenic enlargement was not recorded.

An exanthem was seen in 19 cases. It was unaccompanied by enanthem, conjunctival congestion, or adenopathy, and was commonest in the sharpest phase of the outbreak when 7 rashes were seen in 14 cases. The appearance of 17 of the rashes in relation to day of disease was: first day, 2; second day, 3; third day, 2; fourth day, 6; fifth day, 3; sixth day, 1. In relation to pyrexia the rash was observed in 11 cases when the temperature was falling, in four when intermitting or remitting, in three when destined to fall within 24 hours, and in one when finally resolved. Where an intermission or remission of temperature occurred in the same patient the rash appeared in relation to the first peak in six cases and the second peak in one case.

In 17 cases the rash was erythematous, in one case mixed erythematous and petechial, and in one solely petechial. The erythema consisted of small pink discrete macules or maculo-papules resembling those of rubella. It always invaded the face, to which it was limited in nine cases, often affecting the cheeks only (Fig. 3), but the chin and mid-forehead were also affected in one or two cases and the whole face in two others. On the face the rash took up to as many as five days to disappear; in such cases the spots became semi-confluent and of a violaceous tint. In these respects it recalled the description of the rash in "fifth disease" (Harries and Mitman, 1951). In six cases it spread on to neck, shoulders, and upper part of the trunk. In two cases (one with trunk involvement) isolated areas of

FIG. 3.—Showing rash limited to the cheeks.

rash were seen in the distal parts of the limbs. In one case (that of the youngest patient, aged 15 months) the rash was generalized. On trunk and limbs the rash tended to be short-lived, often altering greatly within a few hours.

In one of the two cases with petechiae these were scattered on the shoulders at the same time as the usual erythematous rash was present on the cheeks; in the other a striking petechial rash appeared in the submental area, with scattered lesions on the trunk and no erythema.

Symptomatic treatment only was given except in one of the more severe cases in which chloramphenicol was used. No complications were observed and convalescence was rapid in all cases.

Clinical Pathology

Fifty-three Specimens of Cerebrospinal Fluid.—Pleocytosis (Table III) did not commonly exceed 500 per c.mm., although it could be much higher. Over the series polymorphonuclears and lymphocytes were approximately equal, with much individual variation. Two C.S.F.s with higher

TABLE III.—*White-cell Counts in 53 Specimens of Cerebrospinal Fluid Taken from 48 Patients (Includes 5 Double Examinations)*

Cells per c.mm.	No. of Samples	Polymorphs Predominant	Lymphocytes Predominant	Polymorphs and Lymphocytes about Equal
0–5 (normal)	5	—	—	—
6–20	2	1	1	0
21–100	11	4	5	2
101–500	28	11	14	3
501–1,000	3	1	1	1
1,001–2,000	2	1	1	0
2,001–3,000	1	0	0	1
3,760	1	1	0	0
Total	53	19	22	7

counts were opalescent and one (3,760 cells per c.mm., 94% polymorphonuclears) was frankly turbid. Repeat lumbar punctures in five patients (four with normal first specimens) all showed marked increase of cells. In about half the specimens a rise of protein above the high normal level of 40 mg./100 ml. was found, usually to less than 100 mg./100 ml., but three cases fell in the range 100–200 mg./100 ml. and there was one of 240 mg./100 ml. (associated with the count of 3,760 cells per c.mm. mentioned above).

White Blood Cell Counts in 33 Patients (Table IV).—About half the counts were either low normal or leucopenic owing to a tendency to relative neutropenia. No example of leucocytosis was found. Atypical lymphocytes were seldom reported. The erythrocyte sedimentation rate (Westergren) was estimated in 18 cases and showed an increase in half the number—three in the range 8–15 mm. in the first hour and six in the range 16–30 mm.

Virus Investigations.—Specimens of faeces from 27 patients were examined at the Virus Reference Laboratory, and in 19 instances a virus related to ECHO virus type 9 was isolated. This experience resembles that found in a number of outbreaks of aseptic meningitis during 1956 (Boissard *et al.*, 1957). In addition, 18 of the patients showed fourfold or greater rises in antibody titre against ECHO virus type 9 during the course of their illness. These laboratory studies will be reported in greater detail separately (A. D. Macrae, to be published).

TABLE IV.—*Total White-cell Counts (Normal, 4,000–11,000 per c.mm.) and Neutrophil Counts (Normal 2,500–7,500 per c.mm.) of 33 Patients*

White Cells per c.mm.	No. of Patients	Neutrophils per c.mm.	No. of Patients
3,000–4,000	5	Under 2,500	7
4,001–5,000	11	2,501–3,000	12
5,001–11,000	17	3,001–9,600	14

Discussion

The occurrence in Coventry in 1956 of aseptic meningitis associated with an exanthem was similar to the experience in a number of other places in that year. A syndrome of this kind had been noted as far back as 1948 (Parry and Good, 1949). The pattern of the Coventry outbreak was consistent with the existence of considerable immunity in the adult and infant populations, children above the age of 2 years being preponderantly affected. The presumed early cases did not have the characteristic rash or the familial incidence of the later ones. These considerations might suggest a variation in the clinical picture of a usually less distinguishable endemic infection.

The Coventry outbreak occurred mainly in one part of the city, and, although it followed the opening of schools for the autumn term, other evidence seemed as much in favour of the home being the theatre of spread as the school. A few cases arose singly in scattered areas in the city but did not give rise to secondary foci, and the factors which encourage the disease to flourish only in one area of the city remain conjectural. It was noticeable that Sonne dysentery was concentrated in the same area, and it is interesting to speculate whether the same environment merely favoured both diseases or whether the causal agent of the meningeal infection profited by the opportunity for faecal spread created by the diarrhoeal disease. There was no clinical evidence that Sonne dysentery predisposed to the meningeal infection, as a history of diarrhoea in the latter was uncommon and in only one household was the coexistence of the two diseases confirmed.

An erythematous rash was observed in every second or third of the Coventry cases and its distribution was characteristic enough to have diagnostic value. The occasional petechial elements and the not uncommon polymorphonuclear predominance in the C.S.F. suggest grounds for occasional confusion with meningococcal meningitis. The occurrence of rashes and of familial cases was commonest at the peak of the outbreak. If the rash can be taken as evidence of viraemia it may indicate that the central nervous system is infected via the blood stream; the development of solid immunity after an attack is also to be expected—as in other virus diseases associated with a rash. The illness was benign and only occasionally acute enough to cause temporary anxiety. Encephalitic signs were absent. Recovery was rapid and complete.

In considering transmission of this type of aseptic meningitis it is tempting to draw a parallel with poliomyelitis. In both diseases virus has been found in pharyngeal washings as well as the faeces—the commonest view in poliomyelitis being that infection may be transmitted at different times by respiratory and alimentary routes (Taylor and Knowelden, 1957). The meningitis outbreak in Coventry occurred in the season favoured by poliomyelitis. Apart from the seasonal predilection, Bradley and Richmond (1953) could not correlate any specific meteorological factor with the incidence of poliomyelitis; likewise the association of a warm spell with the peak of the Coventry outbreak of meningitis may have been fortuitous, but it at least encouraged the mixing of children. Familial illnesses in poliomyelitis are uncommon compared with the frequency seen in this meningeal outbreak, but this may be misleading, as inapparent family infection is not uncommon in poliomyelitis (Francis, 1952).

Summary

In 1956 there were outbreaks in this and other countries of aseptic meningitis associated with an exanthem in a proportion of cases. One of these occurred in Coventry and 51 cases were admitted to hospital. From 19 out of 27 cases a virus related to ECHO virus type 9 was isolated, resembling the experience in a number of other outbreaks in 1956. Eighteen of these cases showed a significant rise of antibody titre to ECHO virus type 9 during their illness.

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The number of cases of plague in the world reported in 1957—namely, 514—was the lowest annual total since the beginning of the century, states the World Health Organization. This is mainly because the incidence in India was unusually low. There were 44 cases there as compared with 262 in 1956, 542 in 1955, and 8,230 in 1951. The world total in 1951 was 15,399. In America, one case was reported in the U.S.A. (Texas) in 1957, and active foci of the disease were detected in Ecuador, Peru, and Brazil. In Indonesia, only 15 cases were notified in Java against 113 in 1956 and 354 in 1955. Most of the cases reported from Asia outside China and the U.S.S.R. were in Burma. In Africa the highest frequency of cases was in the north-eastern part of the Belgian Congo. Sporadic cases were also reported in Kenya, Tanganyika, and South Africa.

PERNICIOUS ANAEMIA TREATED ORALLY WITH "BIFACTON"*

REFRACTORINESS TO POTENT ANIMAL INTRINSIC FACTOR

BY

J. B. STOKES, M.B., M.R.A.C.P.

AND

W. R. PITNEY, M.D., M.R.A.C.P.

Department of Haematology, Royal Perth Hospital, Perth, Western Australia

The underlying defect in pernicious anaemia is a severe deficiency of intrinsic factor secretion by the glandular epithelium of the fundus and body of the stomach. This results in decreased absorption of dietary vitamin B_{12} to an amount less than the body requirement. Body stores are utilized and eventually depleted. The serum vitamin B_{12} concentration then falls below normal and megaloblastic erythropoiesis with an associated macrocytic anaemia results.

The certain diagnosis of pernicious anaemia can be made only by demonstrating reduced secretion of intrinsic factor of sufficient degree to impair vitamin B_{12} absorption.

When a small oral dose of radioactive vitamin B_{12} is given to a patient with pernicious anaemia impaired absorption can be demonstrated by several methods. If the radioactive dose is given with a source of intrinsic factor normal absorption occurs. For the purpose of such tests either human gastric juice or partially purified preparations from hog stomach or duodenal mucosa have been used successfully as sources of intrinsic factor. Radioactive vitamin B_{12} absorption tests make it possible to establish the diagnosis of pernicious anaemia even in patients who are in haematological remission, and for this reason have a wide application in the investigation of patients with megaloblastic anaemia.

It is more convenient to use animal intrinsic factor preparations than human gastric juice in performing radioactive vitamin B_{12} absorption tests. In this communication we present the findings in a patient with pernicious anaemia previously treated by an oral vitamin B_{12}–intrinsic factor preparation who showed impaired absorption when the radioactive vitamin B_{12} was administered orally with hog intrinsic factor. This intrinsic factor preparation regularly promotes normal absorption of radioactive vitamin B_{12} in patients with pernicious anaemia. Our patient absorbed radioactive vitamin B_{12} normally when the dose was given with human gastric juice. The phenomenon of refractoriness to animal intrinsic factor following oral therapy has been observed recently by Schwartz *et al.* (1957).

Materials and Method of Investigation

We have employed a modification of the urinary excretion test (Schilling, 1953) to demonstrate absorption of radioactive vitamin B_{12}. At present we believe the urine test to be the most readily applicable to clinical problems. Mollin and Baker (1955) showed that in some subjects an injection of carbachol (carbamylcholine chloride) increases the secretion of gastric intrinsic factor, and we use carbachol routinely in our modification of the test. We collect urine for 48 hours after the oral dose of radioactive vitamin B_{12}, since Ellenbogen *et al.* (1955) have shown that considerable amounts of radioactivity may be excreted on the second day. The test is carried out in the following manner:

The patient fasts for at least four hours prior to the test and for one hour after the oral dose of radioactive vitamin B_{12}. Fifteen minutes after an intramuscular injection of 0.25 mg. of carbachol the patient drinks 0.6 μg. ^{60}Co vitamin B_{12} (specific activity 0.24 μC./μg.) in 10 ml. of water. Then 1 mg. of non-radioactive vitamin B_{12} is immediately injected intramuscularly and urine collected for 24 hours. At the end of 24 hours a further 1 mg. of non-radioactive vitamin B_{12} is injected intramuscularly and urine collected for a further 24 hours.

Radioactivity of 100-ml. samples of urine is measured in an annular type scintillation counter and urinary radioactivity expressed as a percentage of the administered dose. If this test shows impaired absorption of radioactive vitamin B_{12}, the dose of ^{60}Co vitamin B_{12} is mixed with 50 mg. of a preparation of hog-stomach intrinsic factor immediately before administration and the whole test repeated. This intrinsic factor (Batch 186-1) is from the same batch as that used by Ellenbogen *et al.* (1955) and Baker and Mollin (1955).

Our experiences with this test are shown in Table I. In 13 of 14 proved cases of pernicious anaemia in relapse, 50 mg. of the intrinsic factor preparation was found sufficient to increase urinary excretion of radioactivity into the range shown by 22 normal subjects.

TABLE I.—*Urinary Excretion Test Following an Oral Dose of 0.6 μg. ^{60}Co Vitamin B_{12} in 22 Normal Controls and 14 Proved Pernicious Anaemia Patients in Relapse*

	No. of Subjects	Percentage Oral Dose Excreted			
		0–24 Hours		0–48 Hours	
		Range	Mean	Range	Mean
Normal controls	22	9–29	16·9	16–36	23·7
Pernicious anaemia patients in relapse:					
Without intrinsic factor	14	0–4	1·4	0–7	2·2
With 50 mg. intrinsic factor	14*	7–20	14·6	12–33	21·3

* 13 of the 14 patients were within the range shown by the normal controls.

The pooled human gastric juice used in this investigation was prepared by continuously aspirating fasting juice from two patients with a duodenal ulcer into a flask immersed in melting ice. *N* NaOH was added at frequent intervals to maintain the *p*H at 7 during collection. The gastric juice was then strained and stored at −20° C. until required.

Case History

On January 8, 1957, a 52-year-old woman was referred for the investigation of an anaemia for which she had received various forms of treatment for six years. Treatment included oral and parenteral iron, injections of liver extract, and recently vitamin B_{12} intramuscularly. Five months before referral parenteral therapy was stopped temporarily while she was treated with "bifacton" tablets,* one three times a day for a period of eight weeks. Thereafter intramuscular vitamin B_{12} was recommenced.

A complete clinical examination failed to reveal any abnormality. Haemoglobin was 12.8 g. per 100 ml.; P.C.V., 43%; leucocytes, 3,900 per c.mm. (55% segmented polymorphs, 38% lymphocytes, 6% monocytes, and 1% basophils). A moderate degree of poikilocytosis and slight anisocytosis of the erythrocytes were found. A fractional test meal revealed histamine-fast achlorhydria.

Urinary Excretion Tests.—The results of these tests are set out in Table II. Vitamin B_{12} absorption was considerably impaired, and doses of 50 mg. and 200 mg. of the hog intrinsic factor preparation (Batch 186-1) were ineffective in significantly increasing vitamin B_{12} absorption. The test was repeated using two volumes of pooled human gastric juice. Urinary radioactivity increased significantly with 50 ml. and fell within the normal range with 100 ml. Thus the diagnosis of pernicious anaemia was established.

*This investigation was assisted by a grant-in-aid from the Royal Australasian College of Physicians.

*Each tablet contains not less than 7.5 μg. of vitamin B_{12} and not less than 18 mg. of hog-stomach intrinsic factor concentrate.

TABLE II.—*Urinary Excretion Test Following an Oral Dose of ^{60}Co Vitamin B_{12} With Varying Amounts of Animal Intrinsic Factor and Human Gastric Juice*

	Percentage Oral Dose Excreted	
	0–24 Hours	0–48 Hours
Animal intrinsic factor:		
Nil	3	3
50 mg.	1	2
50 mg.	Nil	1
200 mg.	3	—
Human gastric juice:		
50 ml.	9	12
100 ml.	12	31

Discussion

The investigation of this patient confirms the observation of Schwartz *et al.* that the effectiveness of animal intrinsic factor may be reduced in pernicious anaemia patients who have been treated orally with preparations containing intrinsic factor and vitamin B_{12}. This phenomenon presents certain difficulties in the interpretation of vitamin B_{12} absorption tests in the diagnosis of pernicious anaemia. If failure to absorb radioactive vitamin B_{12} when given with animal intrinsic factor occurs in a patient previously treated orally, it would be advisable to repeat the test, using human gastric juice. It seems possible that other patients reported in the literature as having a selective malabsorption to the vitamin B_{12}–intrinsic factor complex may also be identified as having pernicious anaemia when reinvestigated using pooled human gastric juice.

It is not yet known how often or how rapidly this phenomenon occurs in such patients. Mollin and Ross (1954) noted in a pernicious anaemia patient on continuous oral therapy with bifacton tablets that the serum vitamin B_{12} level fell after approximately six months. In a patient of Schwartz *et al.* the values for the haemoglobin and red-cell count, while never normal during the successful period of oral therapy, began to fall after about eight months. In our patient, bifacton tablets were taken for a period of eight weeks.

In the treatment of pernicious anaemia patients, whether in a state of relapse or remission, it appears that parenteral therapy with vitamin B_{12} is undoubtedly the more certain method and is therefore to be preferred.

Summary

The results of radioactive vitamin B_{12} absorption tests using hog stomach and pooled human gastric juice as sources of intrinsic factor are presented in a pernicious anaemia patient previously treated with bifacton tablets. It was shown that potent animal intrinsic factor did not increase vitamin B_{12} absorption in this patient. However, normal absorption occurred when human gastric juice was used as the source of intrinsic factor.

The implication of this phenomenon in the future investigation and management of pernicious anaemia patients is discussed.

Our thanks are due to Dr. E. Lester Smith, of the Research Department, Glaxo Laboratories, Middlesex, England, who supplied the ^{60}Co vitamin B_{12}, and to Dr. Leon Ellenbogen, of the Research Division, Lederle Laboratory, N.Y., for the intrinsic factor concentrate.

Addendum

Dr. Ellenbogen supplied a more highly purified hog intrinsic factor preparation for trial on the patient. 5 mg. of this material is at least as potent as 50 mg. of Batch 186–1 in potentiating the absorption of radioactive vitamin B_{12} in patients with pernicious anaemia. The urinary excretion test was repeated on the patient, using the purified intrinsic factor, and was still abnormal. After an oral dose of 0.6 μg. of ^{60}Co vitamin B_{12} and 5 mg. of the purified material, 6% of administered radioactivity appeared in the urine in 48 hours. Three patients with pernicious anaemia in relapse excreted between 23% and 30% of administered radioactivity when tested with the same dose of purified intrinsic factor.

To investigate the possibility that the patient's gastric juice contained a substance inhibitory to hog intrinsic factor, 75 ml. of gastric juice was mixed with 5 mg. of purified intrinsic factor. This was administered to a patient with known pernicious anaemia in remission, together with 0.6 μg. ^{60}Co vitamin B_{12}. The pernicious anaemia patient excreted 15% of the radioactivity in the urinary excretion test. When the radioactive vitamin B_{12} was given without intrinsic factor the urinary radioactivity in this patient was 2%.

Immunological studies using the patient's serum and hog intrinsic factor have not demonstrated the presence of circulating antibody.

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Medical Memoranda

Infected Facial "Cysts" and Sinuses of Dental Origin

An acute pulp infection of a tooth or root fragment is usually a painful event that demands urgent relief. Occasionally, however, the pulp undergoes a slow and silent degeneration without symptoms and without producing any visible change in the mouth. There is only an apparently sound and filled tooth, or a gap where a tooth was extracted months or even years ago, and a forgotten root fragment has become infected. In either case it would pass unnoticed at a routine dental examination unless a dental *x*-ray film was taken, where it would be clearly revealed.

After a variable period of chronic infection pus discharges through the thin outer alveolar plate into the mouth, or through into the soft tissues of the cheek. There is then left an established sinus from the infected tooth or retained root, either into the mouth or into the soft tissues. In the latter case a cystic swelling appears in the cheek, which can persist for weeks or months and is similar in appearance to a low-grade infection in a sebaceous cyst. Often it is treated as a simple cyst, by excision, and is followed by a chronic discharging sinus. The communicating track between the cystic swelling and the primary focus of infection is not necessarily the shortest distance between the two, and an oblique or variable course of the communicating track can be a misleading feature.

FIG. 1.—Chronic infected facial cyst.

These cases generally come to us because we are expected to deal with the presenting facial lesion with the minimum of scarring, not because of the dental condition, as this has been overlooked. Obviously, any attempt to treat the facial lesion without first removing the dental focus is a waste of time. Sometimes we are able to deal with both the dental and the facial conditions simultaneously, although occasionally it is advisable to clear the dental focus before tidying the face.

A TYPICAL CASE HISTORY

A perfectly fit schoolgirl aged 14 developed a small cystic swelling on the outside of her right cheek six months previously (Fig. 1). It had been painless throughout, and after its initial appearance had remained fairly constant in size. She was seen by a consultant, who considered it to be a sebaceous cyst and treated it with carbon dioxide snow. She was referred for plastic-surgical opinion. Examination within the mouth revealed a communicating track between the cyst and the alveolus of the upper six tooth. The teeth themselves appeared healthy, and the upper six had a filling which had been put in a year previously. There was no history of toothache. *X*-ray examination showed a quite definite root infection (Fig. 2).

FIG. 2.—*X*-ray appearance of root infection.

FIG. 3.—Showing chronic pulp infection.

Treatment.—Under general anaesthesia the upper six tooth was extracted; the photograph shows the chronic pulp infection with a large granuloma on the palatal root (Fig. 3). The cyst was incised and found to contain necrotic granulation tissue. Between the cyst and the alveolus was a well-defined track, and a probe inserted through the cheek presented in the base of the tooth socket. Culture of the cyst content was sterile. The facial wound healed in three days.

Comment.—Although this condition is commonplace in plastic surgery units, experience of our own cases has shown that many doctors are unaware that a silent dental infection can produce this type of lesion; hence many unsuccessful operations, aimed only at the external end of the trouble, are carried out. A dental opinion and *x*-ray examination should be a routine in all doubtful cases.

D. C. BODENHAM, M.B., F.R.C.S.Ed.
W. BAKEWELL, L.D.S.

Agranulocytosis following Dapsone Therapy

Dapsone (diaminodiphenyl-sulphone, D.A.D.P.S.) has been extensively used in the treatment of leprosy, and to-day it is considered to be the drug of choice for this disease. It was not until as recently as 1950 that Esteves and Brandão drew attention to the beneficial effects of dapsone in the treatment of dermatitis herpetiformis. Since their original publication many observers, including Cornbleet (1951), Kruizinga and Hamminga (1953), Calnan (1954), Anning (1954), Vickers (1954), and Alexander (1955), have confirmed their findings, and dapsone is now recognized as a most valuable agent in the treatment of dermatitis herpetiformis.

The dosage of dapsone recommended has been variable, ranging from 50 mg. daily to 200 mg. daily. However, all are agreed that the dosage should be related to the clinical response, and when this has been achieved it should be replaced by a maintenance dose sufficient to suppress the clinical manifestations of the dermatosis.

The side-effects have been collected and are recorded in Table I.

Detailed investigations of the white-cell series in relation to the use of dapsone are few, and this has been confirmed by a personal communication with the manufacturers. It seems surprising that such an investigation has not appeared as a step in the preliminary therapeutic trials of this drug, which is closely related chemically to the sulphonamides. Calnan (1954) mentions agranulocytosis as a definite indication for cessation of therapy, but does not elaborate by a case history report. Fernandez *et al.* (1948) studied the effect on the cells of the white-cell series when dapsone was used in the treatment of leprosy, and found that the leucocyte count was either normal or indicated an increased granulopoiesis in the bone marrow. Lowe and Davey (1951) in a four-year therapeutic trial of the sulphone drugs, also in the treatment of leprosy, noted as the only white-cell abnormality an initial polymorphonucleosis, latterly mononucleosis, and other features suggestive of a sulphon-induced glandular fever.

Since no previous instance of agranulocytosis has been reported, we put the following case on record.

CASE REPORT

A single woman of 62 was referred to the Department of Dermatology, Western Infirmary, Glasgow, on March 19, 1956, suffering from dermatitis herpetiformis of three years' duration involving the arms, legs, back, and shoulders.

Treatment with dapsone, 50 mg. daily, was prescribed, and the patient was instructed to increase the dosage to 100 mg. in a week's time. She was seen again on April 4, and, although there was a definite clinical response, the condition was not yet under control, and the dosage was increased to 125 mg. daily.

On or about April 16, whilst on holiday, the patient developed an "influenza-like illness," and from that date until her admission to hospital two weeks later she was subject to listlessness, anorexia, periodic vomiting, sore throat, and night-sweating. A blood examination on April 16 (Royal Alexandra Infirmary, Paisley) revealed Hb, 12.2 g. per 100 ml. (84%); P.C.V., 36%; M.C.H.C., 33%; and the peripheral blood film showed no abnormality. On returning home her family doctor stopped dapsone therapy (total dosage, 4.2 g.) because of her general condition and also because a blood count carried out by him revealed a picture suggestive of agranulocytosis. She was admitted to Professor Wayne's wards, Western Infirmary, Glasgow, on April 30, where the diagnosis was confirmed.

On admission she was a rather drowsy woman showing the clinical features of dermatitis herpetiformis, and her temperature was 103° F. (39.4° C.) and B.P. 120/45. Purpuric lesions were present over the shoulders and arms, and the mucosae were uniformly pale. Bilateral ankle oedema and exertional dyspnoea were the only other features noted on examination of the cardiovascular and respiratory systems. The liver, spleen, and lymph nodes were not demonstrably enlarged.

Investigations.—The blood findings are recorded in Table II. The peripheral blood films showed severe leucopenia with the neutrophils virtually absent. The red cells were of normal size and well stained, while the platelets were not obviously deficient in numbers and no primitive cells of either the white or red cell series were present. The direct Coombs test was negative; blood cultures were negative; the augmented histamine test meal showed free acid to be

TABLE I.—*Side-effects*

	Blood	Skin	Mental	Allergic		General	Liver	Nervous
Lowe and Davey (1951)	Anaemia, haemolytic nutritional; methaemoglobinaemia	Sulphone dermatitis	Psychosis	Erythema nodosum leprosum	Sulphone-induced glandular fever			
Cochrane *et al.* (1949)	Anaemia, non-specific					Giddiness; nausea; vomiting	Liver toxicity	Peripheral neuritis
Molesworth and Narayanaswami (1952)		Allergic dermatitis					Jaundice; liver toxicity	Neuritis
Muir (1952)	Anaemia, reactive ? allergic							
Howell (1953)	Anaemia, aplastic					Nausea; vomiting	Hepatitis, allergic	
Calnan (1954)	Anaemia; mentions agranulocytosis		Depression			Headaches		
Cornbleet (1951)	Anaemia; haematuria; leucopenia	Drug rashes						
Alexander (1955)			Depression			Nausea		
Morgan *et al.* (1955)	Transient anaemia; no serious effects on blood							
Ramanujam and Smith (1951)	Haemolytic anaemia; methaemoglobinuria; bilirubinaemia						Jaundice	
Jelliffe (1951)		Urticaria; dermatitis		Unilateral phlyctenular conjunctivitis			Jaundice; fever	
Allday and Barnes (1951)	Hypochromic anaemia	Dermatitis	Delusional insanity	Lepra reactions	? Induced glandular fever		Liver damage	Neuritis

TABLE II.—*Blood Findings*

	White Blood Cells per c.mm.	Polymorphs	Eosinophils	Small Lymphocytes	Large Lymphocytes	Monocytes	Hb g. 100 ml.	P.C.V.	M.C.H.C.	E.S.R.
14/4/56							12·2	36%	33%	
30/4/56	1,500	0	0	900 (90 smear cells)	210	300	8·9	28%	31·7%	
11/5/56	6,100	1,952	0	3,599	0	549	10·4	36%	28·9%	6 mm. hr.
18/5/56	8,800	4,488	88	3,080 (88 smear cells)	440	616	12·6	40%	31·2%	16 ,,
27/8/56	7,900	3,239	948	3,239	79	395	13·6	42%	32·4%	

present after histamine; the urine contained a few granular casts; urobilinogen and acetone were present.

Treatment and Progress.—The patient was treated with 500,000 units of crystalline penicillin six-hourly from April 30 to May 14, and on admission a fresh whole-blood transfusion of two pints (1.14 l.) was given within two to four hours of withdrawal from the donor in the hope of obtaining cells of the white-cell series in a vital and active state. On May 2 sternal marrow puncture showed a picture typical of agranulocytosis of the aplastic type. Mature white cells were absent and their precursors virtually absent, while there was no apparent diminution in the red-cell precursors. The megakaryocytes were not reduced.

The patient made an uneventful recovery and was discharged from hospital on May 18. At a follow-up on August 27 the peripheral blood film showed the eosinophilia usually found in dermatitis herpetiformis and normocytic normochromic haemopoiesis. Both the platelets and reticulocytes were within normal limits. The sternal marrow revealed normal erythroblastic haemopoiesis and normal maturation of the white-cell series. Sections of the marrow fragments showed no hyperplasia. Two lymphoid follicles were present in the stained marrow sections.

COMMENT

From the sternal marrow and peripheral blood examinations on admission there appeared to be a normal erythroblastic red-cell maturation and platelet production. The agranulocytosis was aplastic in type rather than a maturation defect. Various authors have described a hypochromic and a haemolytic form of anaemia associated with dapsone therapy. The anaemia in our case did not appear to conform to either of these types. It was probably due to a toxic depression of the bone marrow of a similar nature to that which produced the agranulocytosis.

We consider this case to be dapsone-induced agranulocytosis for several reasons. Dermatitis herpetiformis does not itself produce agranulocytosis, and there was no recent contact with any other drug known to produce agranulocytosis; the onset of the disease was rapid; complete recovery followed the withdrawal of the drug; the agranulocytosis was of aplastic type.

We wish to thank Dr. R. Massey for bringing this case to our notice, and Professor E. J. Wayne for his help and permission to publish this case. We also thank Dr. Hutchison for his assistance with the haematological findings.

WILLIAM B. MCKENNA, M.D.,
A. C. CHALMERS, M.B., Ch.B.,
Western Infirmary, Glasgow.

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Reviews

BIOCHEMICAL DISORDERS IN DISEASE

Biochemical Disorders in Human Disease. Edited by R. H. S. Thompson, M.A., D.M., and E. J. King, Ph.D., D.Sc., F.R.I.C. (Pp. 843+xiv; illustrated. 90s.) London: J. and A. Churchill Ltd. 1957.

For many diseases morbid histology and anatomy can be effectively supplemented by or replaced by morbid biochemistry. Although this is no new development, the aetiology of relatively few diseases could until recently be interpreted in terms of a disorder of known biochemical reactions. But the rapid development in recent years of the application to disease of the theory and methods of biochemistry has made possible a much more general approach to the consideration of the problems of pathology in terms of those of biochemistry. There is now a wide range of diseases in which abnormalities of enzyme action, congenital or acquired, or deviations from normal of the electrolyte balance of the body cells or intercellular fluids, have been demonstrated. Because certain diseases lend themselves more readily than others to analysis in terms of biochemical entities, this book necessarily treats some diseases more fully than it does others. To illustrate the scope and authority of the book no better method could be found than to give the titles and authors of the twenty chapters: "Diseases of the Gastro-Intestinal Tract" (D. A. K. Black), "Diseases of the Liver and Biliary Tract" (N. F. Maclagan), "The Anaemias" (Sheila T. Callender and J. R. P. O'Brien), "Diseases of the Blood, the Clotting Mechanism" (R. G. MacFarlane), "Hypertension" (G. W. Pickering and W. S. Peart), "Diseases of the Kidney and Genito-urinary Tract" (M. D. Milne), "Adrenal Diseases" (J. W. Jailer and D. Longson), "Diseases of Iodine Metabolism" (J. Wolff and R. Goldberg), "Diseases of Bone and the Parathyroid Gland" (Russell Fraser and E. J. King), "Diseases of the Nervous System" (R. H. S. Thompson and J. N. Cumings), "Diseases of Muscle" (J. L. Lilienthal, jun., and K. Zierler), "Diabetes Mellitus and Hypoglycaemia" (P. H. Forsham and G. E. Mortimore), and "Disorders of Nutrition" (R. Passmore and A. P. Meiklejohn); then come six chapters under the general heading "Miscellaneous Disorders of Metabolism": I. "Some Abnormalities of Amino-acid and Haemoglobin Metabolism" (H. Harris), II. "Connective Tissue Disorders" (E. G. L. Bywaters and L. E. Glynn), III. "Porphyrias" (C. H. Gray), IV. "Haemochromatosis" (S. Granick), V. "Glycogen Storage Diseases and Galactosaemia" (Dorothy H. Andersen), VI. "Lipidoses" (S. J. Thannhauser); and finally, "Disorders of the Reproductive Organs" (P. M. F. Bishop and I. F. Sommerville).

The authors of the book represent both sides of the Atlantic, but the variety of styles and writing has been ably fused into a coherent whole by the two editors. This is a book in which biochemists and physicians alike will find much of interest and of use. It provides in a readable and authoritative manner an account of important aspects of the scientific background of present-day medicine.

F. G. YOUNG.

ESSENTIALS OF NUTRITION

Essentials of Nutrition. By Henry C. Sherman, Ph.D., Sc.D., and Caroline Sherman Lanford, Ph.D. Fourth edition. (Pp. 505+xii; illustrated. 34s. 6d.) New York and London: Macmillan Company. 1957.

The new edition of this excellent book has been revised with the double objective of bringing the contents up to date and improving, where possible, the clarity of presentation. It attempts the difficult task of teaching the fundamentals of nutrition to readers who may have had no training in science. Each of its 21 chapters, which cover all aspects of the subject from energy requirements to vitamins and trace elements, is rounded off both with a series of questions to test the conscientious student and with a brief selection of references for further reading. Even plans for practical experiments with animals are suggested. Appendices include tables giving the composition and nutritive value of foods and recommended dietary allowances. Teachers of nutrition will admire the well-ordered presentation of the subject-matter in this book and the clarity of the language. They may doubt, however, whether it is possible to convey more than a very superficial knowledge of the science of nutrition to students who have no grounding in medicine and chemistry. To help the uninitiated an excellent glossary is included. But a statement, for example, that vitamin E may take part in the cytochrome C reductase system will not mean much to readers whose knowledge of biochemistry is inadequate. Perhaps we may conclude that the authors are not seeking perfection but are facing facts. Many students, with different educational backgrounds, are doubtless called upon to acquire at least an elementary knowledge of nutrition as a help in their employment as teachers, nurses, or public-health workers. This book aims at the instruction of the average member of this wide range of readers, and at the same time includes additional information for those who are capable of its assimilation.

T. MOORE.

ARTIFICIAL INSEMINATION

Artificial Insemination in the Human. By A. M. C. M. Schellen, M.D. Introduction by Sophia J. Kleegman, M.D. (Pp. 420+xii. 72s.) Amsterdam, Houston, London, New York: Elsevier Publishing Company. 1957.

When Dr. Schellen was writing this book he could hardly have known that its arrival in Great Britain would coincide with a renewed interest by the lay press in "test-tube babies." He did realize, however, that, despite the difficulties and disputes which encompass it, artificial insemination with donated semen is being increasingly practised in certain parts of the world. Indeed, he quotes an estimate of there now being 100,000 individuals in the U.S.A. who were conceived as a result of this procedure.

The author produces evidence to show that A.I.H. was probably first carried out by John Hunter, the indication being male hypospadias, and that A.I.D. in the human originated in Philadelphia in 1884. The further history of both these methods together with their indications, techniques, dangers, results in terms of both human happiness and pregnancies, legality in various countries, and their moral, genetic, ethical, and religious aspects are all considered. The need for secrecy, the choice and payment of donors, and the views of the medical profession, the laity, and the popular press also receive attention. Other matters of detail which are intriguing include the incidence of abortion and the sex ratio among foetuses conceived as a result of artificial insemination. Indeed, there is no facet which seems to have been omitted, and its factual information, combined with a large bibliography, makes this exhaustive treatise a reference book of the highest value.

All the matters mentioned above, and others besides, are presented with admirable detachment, and, except that there is no mention of any results from the author's practice, the reader can reach the last chapter without knowing whether Dr. Schellen is for or against artificial insemination. The reader is also likely to reach it with the conclusion that, judging as objectively as possible what Dr. Kleegman calls an "emotionally charged area," the advantages of A.I.D. do not outweigh its disadvantages to the patient, the offspring, and the community. That this is the result he desires, Dr. Schellen makes abundantly clear in an epilogue in which his previous painstaking scientific restraint is replaced by an emotional outburst against A.I.D. (and presumably A.I.H. as well) on grounds of religion and morality. Passionless conception has already aroused too much passion, and it is unfortunate that an otherwise excellent

book discloses, in the end, this failing. The epilogue weakens rather than strengthens the author's case. Indeed, it makes a case appear to be a cause, and this cannot but serve to raise doubts, probably quite unjustifiable, about the impartiality of the evidence which goes before.

T. N. A. JEFFCOATE.

DISORDERS OF THE VOICE

The Voice and its Disorders. By Margaret C. L. Greene, L.C.S.T. (Pp. 224+ix; illustrated. 45s.) London: Pitman Medical Publishing Co., Ltd. 1957.

This book is written by a speech therapist mainly for the use of speech therapists, but laryngologists and general practitioners will find that it contains much useful information from their standpoint. Evidently the author has had help with the purely medical and surgical portions of the work from her colleagues at the Royal National Ear, Nose, and Throat Hospital and the Plastic Surgery Unit, Stoke Mandeville Hospital, gratefully acknowledged in the preface, and which adds considerably to the value of the book.

The anatomy and physiology of the vocal organs are fully described and the functions of respiration and vocalization well discussed. There follows an account of many forms of voice disorder, which include the effects of vocal strain and vocal abuse, with observations on the causation, symptoms, and appropriate treatment. Then come chapters on hysterical disorders of the voice, disorders of pitch, and the nasal dysphonias, the terms "nasal" and "denasalized" being preferred to "hyper-rhinolalia" and "hypo-rhinolalia" respectively. Incidentally, in connexion with palatal palsies, reference is made to the Rosenthal type of operation, in which a flap from the posterior pharyngeal wall is attached to the edge of the soft palate; the more frequent procedure of palatoplasty or so-called "push-back" operation on the soft palate is not mentioned. The causes of laryngeal paralyses, including upper and lower motor neurone lesions, are discussed, and subsequent chapters are devoted to the subjects of intralaryngeal disease, tumours of the larynx, and the care and treatment of the patient who has undergone laryngectomy, with observations on oesophageal speech.

Many excellent communications on various disorders of the voice are scattered in different medical journals and sundry textbooks, to which Mrs. Greene's ample bibliography of 123 references testifies, but there has previously existed no comprehensive account of the normal vocal mechanism and disorders of the voice contained in a single volume handy for reference; also there is a good index. No speech therapist can afford to be without this book for frequent reference.

C. WORSTER-DROUGHT.

RHEUMATIC DISEASES

Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich G. Brugsch, M.D., F.A.C.P. (Pp. 330+xiv; illustrated. 80s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1957.

The author states in his preface that this book "has been written from an internist's point of view to provide the practising physician and postgraduate student with a concise and readable introduction to the field of rheumatology." The result is a readable and well-produced volume on this subject—a subject which is attracting into its field an increasing number of authors of varying skills. He goes on to say that "the faults of omission . . . are compensated for by the addition at the end of each chapter of a selected bibliography which should serve as a guide for those wishing to study specific problems more thoroughly." It is surprising, therefore, to find that amongst these there is only very occasional reference to European medical literature—particularly strange as rheumatology is one of the young medical specialties which underwent its gestation period in Europe, where the author states that the first thirty years of his life also were spent.

The best portions of this book are the clinical descriptions of the various disease syndromes, although perhaps more space could with advantage have been given to the section on the diffuse collagen diseases. Writing of ankylosing spondylitis, it is interesting to note that, unlike the native American authors, who mostly assume this disease to be a variant of rheumatoid arthritis, he states that "certain characteristics of the disease suggest that we are dealing with a disease entity," a viewpoint which would meet with universal acceptance in this country.

W. S. C. COPEMAN.

PLASTIC ARTERIAL GRAFTS

Plastic Arterial Grafts. By W. Sterling Edwards, M.D. (Pp. 126+xi; illustrated. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

Since the successful introduction by Voorhees in 1952 of the plastic-cloth replacement of arteries a large variety of materials have been used. The majority give satisfactory results in the aorta, but a satisfactory plastic prosthesis to replace the femoral artery has yet to be found. Many materials, particularly "terylene" ("dacron"), give promise, but no adequate follow-up has yet shown that these materials will remain open for as short a time as one year in as few as 50% of patients. In this monograph Dr. Sterling Edwards reviews his experience with the crimped nylon prosthesis which he introduced. For replacement of the abdominal aorta the results have been satisfactory in the four of his five patients who survived the operation, but for peripheral vessels the results have been less satisfactory. In 20 limbs a femoral or iliac by-pass graft was inserted; five occluded immediately and one became partially detached at the femoral suture line after four months. The full follow-up on the other 14 patients is not given, but one prosthesis was clinically patent eighteen months later. In six patients an aortic-iliac or aortic-femoral by-pass was inserted: five left hospital with patent prostheses, but the longest follow-up is only five months.

This well-written monograph must, as the above figures indicate, be taken as an interim report on one method of plastic blood-vessel replacement, and as such it is valuable; but the last word has not yet been written on this subject, and Dr. Edwards, when commenting upon the replacement of obstructed femoral, popliteal, or iliac segments, states: "Sufficient time has not passed to allow evaluation of the crimped nylon tube in this regard, but it would not be surprising to us to discover that the incidence of late thrombosis is similar to that with homografts and vein grafts." If this proves to be correct, the crimped nylon prosthesis will replace the homograft because it is easier to obtain.

This book is recommended to those interested in the plastic replacement of blood vessels, but this field is changing so fast that further reference to the literature is already required.

C. G. ROB.

The deleterious effect of tobacco smoking on health has become a matter of importance to every doctor. A collection of statistics showing how much is smoked in Great Britain and a number of other countries is therefore welcome. It has been prepared by Mr. G. F. Todd for the Tobacco Manufacturers' Standing Committee, and it seems admirably to fulfil the committee's primary object, which is "to assist research into all questions on the relationship between smoking and health." Tables show average and total consumption of tobacco, subdivided by how it is smoked (cigarette, pipe, etc.), for years back to 1920 and in some cases further. Some replies from sampled populations show that about 77% of men smokers and 44% of women smokers began smoking before they were 20, and the frequency of inhaling increased with the amount smoked. A limited number of copies of this book are available for research workers, who should apply to the Tobacco Manufacturers' Standing Committee, 6-10, Bruton Street, London, W.1.

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ACUTE OTITIS MEDIA

A recent Medical Research Council report[1] shows that general practitioners are treating acute otitis media with a high degree of success. A survey was carried out during 1955 by twenty-eight doctors in thirteen practices, some single-handed, in various parts of the country. The National Health Service population covered by these practices amounted to more than 47,500 patients, of whom 11,277 were children under 15 years of age. In this population there were 1,323 attacks of acute otitis media during the year, yet only 14 cases were referred for hospital treatment. The findings confirm the known high incidence of the disease in childhood, particularly in children aged 2–14 years; these accounted for more than 85% of the attacks. The highest attack rates were in those aged 3–6; the incidence rose to nearly 21% in the 6-year-olds. Thereafter there was a sharp decline with increasing age to 3% at 14 years, 1% for adolescents and young adults, and only 0.2% among patients aged over 65 years. Almost half the cases occurred during the first quarter of the year, with a sharp decline to the lowest incidence in August. In the autumn the numbers slowly increased, but the December figures were well below those of the peak period. Excluding the infants under 2 years of age, more than half the patients had had previous attacks of otitis media. Such data as were obtained on the significance of tonsillectomy and adenoidectomy in relation to recurrence of acute otitis media showed no difference that could be attributed to the operation. While pain and redness of the drum were the most frequent diagnostic features, discharge was present in only a quarter of the attacks in the children aged 2–14 years, but occurred more frequently in the infants and the older patients. The mean duration of the illness was 11 days and the median duration 7 days. The study was in no way planned to be a clinical trial of the methods of treatment carried out by the practitioners taking part. Sulphonamides or antibiotics (mostly penicillin) were used in 80% of the cases, 41% being treated with oral antibiotic, 27% with parenteral antibiotic, and 27% with sulphonamides. There were wide differences in individual practices; in some only 40% of the cases received any of these treatments. How successful these methods of treatment were is shown by the small number of complications, amounting to 8 cases—including one death from meningitis 49 days after the onset of the otitis and one case requiring mastoidectomy. Seventeen patients, of whom only 2 were children, were found to have persistent discharge from the ear when seen six months after the onset. Less satisfactory was the discovery of deafness in nearly 4% of the children and 17% of the older patients, but in general it seems to have been slight and possibly temporary in the children and probably of longer standing in the adults.

While the report is of interest in showing the value of research in general practice and of the results that may be obtained by placing on record the pattern of the disease and the effects of treatment, it unfortunately gives no indication of the effects of the various types of treatment used, particularly parenteral and oral penicillin, sulphonamides, or local treatment only. The results would have been of great practical value if they had indicated the relative efficiency of the treatments most in favour at the present time. The report suggests a further investigation. This is certainly necessary, but time would elapse before the results were available. In the meantime would it not be possible for the committee to re-examine their records and publish any results which they may contain?

Though the incidence of acute otitis media has changed little in the past two decades there is no doubt that the course of the illness is to-day greatly reduced in severity and duration. Fewer patients are now being admitted to hospital for mastoidectomy. G. F. Abercrombie twenty years ago found that 10% of 86 patients required mastoidectomy, while less than 0.1% did in the present survey. More than three-quarters of the attacks now last less than a fortnight. There is no doubt that modern treatment will prevent or control the serious complications of acute ear disease to a degree unheard of in the previous generation. But as a recent memorandum from the Ministry of Health[2,3] points out, a large number of young people are either not seeking treatment soon enough or are not persevering with it. J. A. H. Lee,[4] in a survey of men rejected for National Service, found that 3% of the candidates were not acceptable on account of ear discharge. However, a high proportion of his cases were due to cholesteatosis (cholesteatoma), a condition not usually a sequel of simple acute otitis media, and of the remainder a high proportion could have been readily cured in the

[1] Report of a Survey by the Medical Research Council's Working Party for Research in General Practice, *Lancet*, 1957, **2**, 510.
[2] *Memorandum on the Prevention and Alleviation of Deafness*, Ministry of Health, 1957, London.
[3] *Brit. med. J.*, 1957, **2**, 153.
[4] Lee, J. A. H., *Publ. Hlth (Lond.)*, 1955, **68**, 102.
[5] Hodgkin, K., *Lancet*, 1957, **2**, 514.
[6] Søhoel, T., *Acta Oto-Laryng. (Stockh.)*, 1955, **46**, 422.
[7] Davison, F. W., *Laryngoscope (St Louis)*, 1955, **65**, 142.
[8] Adams, W. Stirk, *J. Laryng.*, 1957, **71**, 565.

early stages by adequate and simple treatment. K. Hodgkin[5] found that more than half (in winter, two-thirds) of his cases of acute suppurative otitis media were due to *Streptococcus pyogenes*. There is thus good reason for routine treatment with penicillin in all such cases. It may be said that acute otitis, whether because of the introduction of treatment by antibiotics and sulphonamides or a coincidental change in the natural pattern of the condition is now a disease with much less serious consequences than formerly, though it still has the important sequela of deafness. However, even in this respect the survey shows the improvement now obtained from treatment compared with the results quoted by T. Søhoel.[6] He followed up a series of cases of acute suppurative otitis media in children aged 1–10 years when treated in hospital between the years 1941 and 1947. Ten years later he found that when the original acute attack had lasted for less than two weeks 95% of the children had regained normal hearing. When the otitis lasted more than two weeks the proportion of deaf cases rose to 25%, and with recurring otitis to as high as 50%.

The M.R.C. survey and Søhoel's paper confirm the opinion that deafness more commonly follows recurrent attacks of otitis, particularly when they do not respond promptly to treatment. Consideration of measures to prevent further attacks is therefore a necessary part of the aftercare. Few will disagree with F. W. Davison,[7] who found that otitis media occurs more often in children with enlarged adenoids; experience in Great Britain would generally confirm that adenoidectomy prevents recurrences in a high proportion of cases. However, removal of the adenoids may not be sufficient when the lymphoid tissue extends around and into the Eustachian tubes. In those cases where there is associated catarrhal deafness due to dysfunction of the Eustachian tubes treatment by radiation has to be considered and is advocated by Stirk Adams.[8] The lower incidence of acute otitis in adults is in part due to the atrophy of this lymphoid tissue, which usually takes place after puberty. Chronic infection of the nasal sinuses is not uncommon in children and will prolong the period of aural discharge. Davison[7] has also found that an allergic or atopic constitution, stated to be present in about 10% of the population, is commoner in cases of acute otitis. Once the ear has been infected, mucosal damage and scarring are apt to diminish the resistance of the tissues of the middle-ear cleft to further bacterial attacks. An unhealed perforation of the drum will predispose to middle-ear invasion from the nasopharynx or external meatus, and here myringoplasty or tympanoplasty will offer an effective cure in many cases.

DETECTING DISEASE

It is a remarkable fact that for knowledge of health we rely largely on information about death. National mortality rates have been in existence for more than a century, but there are few good data on morbidity, and other more direct indices of health scarcely exist. Yet mortality statistics are in many respects an unreliable guide to the incidence or social consequences of diseases; for example, they would lead us to overestimate the significance of cancer of the lung and to greatly underestimate the significance of the common cold. Unfortunately it is easier to recognize these difficulties than to remedy them. Death is a single event for which an immediate cause can frequently be given. Many episodes of sickness meet neither of these requirements, and it is not surprising that it is only for a group of notifiable infectious diseases that continuous records are available for any considerable period.

In the absence of national data many attempts have been made to obtain information about sickness by *ad hoc* inquiry. The investigations of Chadwick and Booth in the nineteenth century had wider objectives, but they contained observations on disease which, if lacking in precision, were sufficiently impressive to exercise a profound influence on public health policy. In 1899 Rowntree began the first of his three notable surveys in York, which were concerned, however, with the level of poverty rather than with its effects on health. Other investigators have examined the incidence of disease in selected occupational or age groups, and from 1912 National Health Insurance records provided a useful complementary source of data about the insured population. But the only comprehensive inquiry so far attempted in Great Britain was the Survey of Sickness conducted by the Government's Social Survey from 1944 to 1951. A random sample of the general population was interviewed and information recorded about sickness and its effects during the preceding months. The sickness survey came to an end in 1952, and much of the information which it provided is not now available from any other source.

Before considering whether this is a serious deficiency we should ask ourselves what this type of investigation can hope to achieve. The relationship between poverty and sickness—the theme of many of the early social surveys—is no longer in doubt, and to be useful the results need to be both more novel and more precise. There are at least three main purposes which the large-scale investigations of morbidity might be expected to serve. They might provide a picture of disease incidence which would be complementary to that obtained from the study of

mortality. They might enable us to assess the social importance of different diseases according to such indices as frequency of medical consultations, days spent at home or in hospital, and the period of absence from work. And by showing the variation in the incidence of disease in relation to influences such as season and social circumstances they might provide valuable clues to aetiology.

To what extent have the large surveys of sickness met these requirements? Although they have varied considerably in objectives and scope, they have usually relied on information obtained from the general public by non-medical interviewers. It is a method which has serious limitations, particularly when accuracy of diagnosis is essential. It is probably a fair assessment of the achievement of inquiries such as the Survey of Sickness to say that they have added little knowledge of aetiology or incidence of specific diseases, and have been most useful in indicating the frequency of minor manifestations of ill-health and in assessing the social consequences of disease. Indeed, the chief criticism of these surveys is that they are expensive in relation to the information they provide. It is perhaps only fair to add that the most expensive of them all, an investigation of morbidity in the United States in the mid-thirties, was undertaken as part of the New Deal programme of public works, whose object was to spend rather than save money. But many other surveys have had the same objection without the same excuse.

In a review,[1] published this week, of the achievement of the Survey of Sickness W. P. D. Logan and E. M. Brooke conclude that the survey method should be used "not as a permanent operation to measure the total load of ill-health, its nature, distribution, and trends, but to contribute, from time to time as the need arises, particular items of information on illness and its effects that cannot readily be obtained in a routine way." This seems the right conclusion. Hospital and National Insurance records provide information which can be supplemented with relatively little trouble or expense from a number of other sources, such as the records of general practitioners. Already a number of studies of general practice have given data on morbidity which it would have been difficult to obtain through any other channel, and when fully developed this source may provide one of the most reliable guides to the state of health of the general population. In these circumstances the *ad hoc* field inquiry would probably be much more useful if concerned with well-defined problems related to specific diseases. It is a notable feature of the British school of social medical research which has developed since the end of the war that attention has been focused largely on individual diseases—bronchitis, cancer of the lung, congenital abnormalities, coronary disease, peptic ulcer, tuberculosis—rather than on the broad study of morbidity which was the subject of earlier inquiries. A comparison of the results leaves little doubt about which is the more rewarding method.

[1] Logan, W. P. D., and Brooke, Eileen M., *The Survey of Sickness, 1943 to 1952*. General Register Office, H.M.S.O., 4s.

ENTEROVIRUSES

It is generally believed now that most cases of benign aseptic meningitis are due to virus infection. It was thought that poliomyelitis virus was responsible for most cases of this disease, but in a paper from Sheffield D. A. J. Tyrrell and colleagues,[1] like many other workers, have found evidence of infection with poliomyelitis virus in only 10 out of 24 cases occurring in 1954. Using similar thorough tissue-culture and serological methods they found evidence of infection by this virus in 15 out of 16 cases of paralytic poliomyelitis. In the remaining 14 cases of aseptic meningitis they found no convincing evidence that the disease was due to infection with Coxsackie or ECHO viruses. From 98 cases of aseptic meningitis occurring in Norway in 1955, O. Lahelle[2] obtained only 12 strains of poliomyelitis virus but 48 isolations of an ECHO virus (a virus which is not a poliomyelitis or Coxsackie virus but is found in human faeces and grows readily in tissue culture). The virus was found in only 2 of 18 cases of other disease and in none of 37 cases of paralytic poliomyelitis, most of which yielded poliomyelitis virus. In the Norwegian epidemic it appeared therefore that a large proportion

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[29] Javett, S. N., *et al.*, *J. Pediat.*, 1956, **48**, 1.
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of cases was due to an ECHO virus, and this was supported by finding rises of serum antibody indicating that the patients suffered an infection at the time of their illness. Most of the ECHO viruses were recovered first from normal children. This sort of controlled and comprehensive study is therefore necessary because, as Tyrrell and his colleagues[1] found, viruses cannot be recovered from many cases of aseptic meningitis, and so the isolation of a virus from the faeces in such cases might be coincidental. Lahelle recovered the virus from the cerebrospinal fluid of about a quarter of his cases, and this is additional strong evidence in favour of its causing the meningitis. The virus was found to belong to type 6, which was associated with cases of aseptic meningitis occurring in the U.S.A.[3,4] and Sweden[5,6] in 1954–5. There are fresh reports of ECHO virus type 4 causing this disease.[7,8] There are also many recent papers which add to the evidence, reviewed in these columns last year,[9] that ECHO virus type 9 caused epidemics of aseptic meningitis, meningitis with a rash, and minor febrile illness in Northern Europe[10–16] and Canada[17] last year, and of aseptic meningitis[18] in Italy the year before. This week Dr. J. F. Galpine and colleagues report at page 319 of the *Journal* another outbreak characterized by vomiting, rash, and meningism, and apparently due to ECHO virus type 9, in which the incidence of cases ran parallel with that of cases of Sonne dysentery. Dr. I. Ash reports (page 316) a similar outbreak in which attempts to determine a virus cause were unsuccessful.

A flood of papers like this introducing more and more virus groups and serotypes tends to confuse and dismay the doctor seeking to increase the precision of his diagnosis and his understanding of disease processes. A similar problem has faced laboratory workers, who have found that their tidy separation of poliomyelitis, Coxsackie, and ECHO viruses is breaking down. For example, Russian workers recovered a "new" poliomyelitis virus which is serologically identical with Coxsackie A virus type 7,[19,20] and American workers have found that Coxsackie A viruses types 7 and 14 may cause poliomyelitis in monkeys.[20,21] Poliomyelitis viruses may cause lesions resembling those produced by Coxsackie B viruses in animals,[22,23] and the ECHO type 9 viruses mentioned above might just as well be classified as Coxsackie A viruses, because most of them cause lesions in suckling mice typical of this group.[10,13,15,17,18,24,25] British[25] and American[26] workers have therefore concluded that poliomyelitis, Coxsackie, and ECHO viruses, which are very similar in their physical properties, should be regarded as one large and varied biological group of organisms, which should be called "enteroviruses." This move from the laboratory suggests that these viruses might be looked at as one group for broad clinical purposes also.

These viruses are all primarily harmless parasites of the human alimentary tract, but they may cause inflammation in the pharynx and minor intestinal disturbances (herpangina, febrile pharyngitis, and the prodromal illnesses). Some occasionally spread to the nervous system causing aseptic meningitis, poliomyelitis, and rarely encephalitis.[27] Some spread less often to striated or cardiac muscle, causing epidemic myalgia or myocarditis of the newborn[28,29] or to skin.[12,13,15,30] But there is hope that in the near future some broad principles and simplifying generalizations may emerge.

HAEMOSIDEROSIS AND HAEMOCHROMATOSIS

Idiopathic haemochromatosis is characterized morphologically by heavy deposits of iron and other pigments in the parenchymal organs and skin, and clinically by diabetes and hepatic cirrhosis. It is a rare disease, at least in Great Britain. The nature of the underlying defect is obscure, but is probably related to a fault in the intestinal mechanism that normally controls the absorption of iron from the food.[1] Owing to the absence of any efficient excretory mechanism for iron, metabolic balance is maintained in man on a daily intake of as little as 1 mg. Since the average English diet provides 5–15 mg. of iron per day, the necessity for efficient control of absorption is obvious. The quantity of iron found in the tissues of patients with haemochromatosis often exceeds the normal by over 50 g., which implies that excessive absorption must have been going on for the greater part or even the whole of the patient's life, a deduction which agrees well with the view that idiopathic haemochromatosis is the result of an inborn error of metabolism.

A problem that still defies solution is the relation in this disease of the excessive deposits of iron to the fibrosis of the organs affected, particularly the liver and pancreas. The widespread administration of parenteral iron and sometimes of liberal blood transfusions in cases of anaemia have given emphasis to our ignorance of the role of iron in the pathogenesis of the cirrhosis. Attempts to produce hepatic cirrhosis in experimental animals by repeated injections of iron preparations have met with uniform failure despite the enormous parenchymal deposits of iron achieved.[2] It appears, therefore, that something more than the sheer weight of iron present is necessary. As a result of a recent study of five cases of transfusional siderosis D. F. Cappell and colleagues[3] have suggested that the source of the exces-

[1] Peterson, R. E., and Ettinger, R. H., *Amer. J. Med.*, 1953, **15**, 518.
[2] Nissim, J. A., *J. Path. Bact.*, 1953, **66**, 185.
[3] Cappell, D. F., Hutchison, H. E., and Jowett, M., ibid., 1957, **74**, 245.
[4] Luongo, M. A., and Bjornson, S. S., *New Engl. J. Med.*, 1954, **251**, 995.
[5] Davis, W. D., and Arrowsmith, W. R., *J. Lab. clin. Med.*, 1952, **39**, 526.

sive iron may be more important than its quantity. Thus, an analysis of 20 published cases of transfusion siderosis showed that 9 were regarded by the authors as having hepatic cirrhosis, but in 8 of these 9 the amount of iron in the liver greatly exceeded that which could have been provided by the blood transfused. In the 11 cases, however, without cirrhosis the iron content of only one exceeded that which could have been derived in this way. The inference drawn by Cappell and his colleagues is that in the cases that developed cirrhosis a fault in the mucosal control permitted excessive absorption of iron from the intestine despite the overload already present in the tissues; and that it is this iron rather than that derived from haemoglobin that is toxic to the liver and pancreas.

Evidence from other sources suggests that iron absorbed in excess from the alimentary canal can damage the liver. Both in animals and man poisoning by overdosage with ferrous sulphate can produce considerable necrosis of the liver cells.[4] Presumably the binding of iron to protein as in normal absorption renders it innocuous, but excessive intestinal absorption in the presence of huge haemosiderin deposits might well prove too much for such a hypothetical detoxication mechanism. That the iron in the liver in cases of haemochromatosis is by no means inert is well shown by the improvement of such patients when the iron stores are drastically reduced by repeated phlebotomies.[5]

BEYOND THE LIMIT

Capital spending in the Health Service, like expenditure on running the Service, is a matter for hard bargaining between the hospital authorities, the Ministry of Health, and the Treasury. The Treasury decides the total amount that can be spent on capital account by the hospitals, having regard to the capital needs and commitments of the country as a whole. To begin with this capital allocation was made on a year-to-year basis, with the result that neither hospitals nor the Ministry of Health could plan their capital programmes with any confidence that they would be fulfilled. In February, 1955, however, a capital plan for the hospitals was announced which laid down the sums that would be made available for two to three years ahead, so that major building projects could be undertaken. But although the promise of definite sums over a longer period enabled the hospitals' building programmes to be better planned and co-ordinated, they still have to be rigorously scrutinized by Whitehall. Most of the sum that has been decided on for the following financial year is divided among the hospital boards, mainly on a population basis, and the boards have to submit for the Ministry of Health's approval their programmes of capital expenditure during the year. This expenditure must be kept within the total laid down for the year, which means that the boards have to keep their capital works under constant review. Nor can they initiate schemes of any size without prior consent. Until November, 1956, this consent had to be obtained for all schemes costing more than £10,000. The Guillebaud committee on the cost of the Health Service had recommended that this limit should be raised to £50,000, but the Treasury compromised by raising it to £30,000. This, however, is not the end of the control. For the bigger schemes the consent of the Ministry of Health is not enough: until November, 1956, the Treasury's approval had to be obtained for those costing more than £30,000, and then the limit was raised to £60,000, though the Guillebaud Committee had suggested £100,000.

The scheme on which the Comptroller and Auditor General, Sir Frank Tribe, commented in his report[1] on the appropriation accounts last week fell into the category that has to have prior approval by the Treasury before it can be initiated. It also, because of its size, fell into the category of schemes that are excluded from a hospital board's normal capital allocation and are financed centrally by the Ministry of Health, which retains for this purpose some of the capital sums decided on by the Treasury. But yet another authority entered into this particular scheme. For it turns out to have been undertaken at the Radcliffe Infirmary, Oxford, some of it to provide additional facilities for the treatment of patients, but some at the request of the university to provide accommodation for, among others, the professors of medicine and surgery. This was regarded as a matter of extreme urgency. The Treasury accordingly blessed building projects for the scheme to the tune of £434,390. This was in the spring of 1955, the university having made its request some time in the previous year. Not unnaturally, as the plans seem to have been drawn up in haste, the original estimate turned out to be far too low. By August, 1956, the cost of the scheme was put at £815,000, and at the time Sir Frank Tribe reported it had risen to over £1 million. But under-estimating was not the only fault committed by the board of governors, for it proceeded with much of the work before the Ministry had approved the details. Moreover, though warned in August, 1956, that this should not happen, the board subsequently accepted a contract for work not covered by the approvals that had been given by that date.

Nobody has suggested that the Oxford scheme is not a good one. The Ministry told Sir Frank Tribe that authority to cover the work, even at the increased cost and in its expanded form, would have been given had it been asked for. But the system of control broke down, and the whole affair provides a good example of how the division of responsibility between those who provide the funds and those who carry out the work can recoil on the taxpayer. The position of the university is also left obscure. Because part of the scheme was not necessary for Health Service purposes, the University of Oxford was to pay £176,500 towards the cost. This sum has now been raised to £202,000, but it is still not known whether this will meet the full extent of the university's liability; it is a much lower proportion of the total cost than was originally allowed for. A university, it should be pointed out, does not have to submit to Whitehall detailed estimates of what it is spending its

[1] *Civil Appropriation Accounts (Classes I-V) 1956-7*. H.M.S.O., London.

grant on. The grants are made quinquennially, and the universities are given a free hand in the spending of them—an independence which other public bodies do not enjoy and which Sir Frank Tribe, as a Government watchdog, has criticized in the past. The board of governors at Oxford may well have found itself in a difficult position between the university, accustomed to freedom from control and determined to have a first-class teaching hospital, and Whitehall, insisting on prior approvals and annual checks.

STEROIDS AND PANCREATITIS

Anyone who studies the literature on steroid compounds must soon become aware that the beneficial effects of therapy may at first sight directly contradict experimental evidence from the laboratory. A recent example of this apparent paradox is the action of steroids on the pancreas. The impression among clinicians is that cortisone and related drugs may be of value in the treatment of acute pancreatitis.[1-3] The mortality rate in this disease has been reported to be as high as 30%, and death is usually due to circulatory failure. It is here that corticoids, and particularly intravenous hydrocortisone, might be expected to be beneficial, and indeed they have been claimed to be life-saving. On the other hand, the disturbing fact has recently come to light that cortisone can produce histological changes in the pancreas similar to those of acute pancreatitis. Two groups of workers[4,5] have noted, in animals receiving cortisone, dilatation and proliferation of intrapancreatic ductules, together with accumulation of inspissated material in the lumina and patchy areas of fat necrosis. F. A. Carone and A. A. Liebow[6] have now studied necropsy material from a consecutive series of 54 patients who were treated with steroids, and they report ductular proliferation in over half and acute pancreatitis and fat necrosis, sometimes severe, in more than a quarter. In spite of the histological evidence, there were no definite clinical indications that the patients had suffered from attacks of pancreatitis. Nevertheless H. S. Baar and O. H. Wolff[7] have recently described two children in whom acute pancreatitis was almost certainly associated with steroid therapy.

The mechanism of this serious disease remains obscure. Such factors as malnutrition, alcoholism, vitamin deficiency, and hyperlipaemia are probably important in only a minority of cases. Pancreatitis can arise as a complication of any of the acute infectious fevers, and particularly mumps. The widespread nature of the necrosis suggests that in some patients interference with pancreatic blood supply may be the precipitating factor. On the other hand, the association, both clinically and experimentally, with infection and obstruction of the biliary and pancreatic ducts is well established. The changes produced in cortisone-treated animals are similar to those found in animals in which the pancreatic duct is ligated,[5] though milder and more patchy. It is possible that steroids produce an intermittent obstruction, due to a change in viscosity of the pancreatic secretions, though infection as a causative factor has not been certainly excluded. The similarity between the lesions produced by cortisone and those of acute pancreatitis suggests a fruitful line of approach to the clinical problem. It is worth emphasizing, however, that the histological effects in animals are the result of prolonged treatment with high doses of cortisone, and that acute pancreatitis is apparently an extremely rare complication of steroid therapy in man. There is at present no reason for withholding corticoids in patients with acute pancreatitis, particularly if there is severe circulatory insufficiency, provided that treatment for pain and shock, electrolyte imbalance, and infection has already been started.[8]

TUBERCULOSIS RISKS IN LABORATORIES

One of the occupational hazards to which doctors are exposed is infection with the numerous pathogenic organisms which their patients exhale or excrete. The special dangers of poliomyelitis were the subject of a report last year,[9] and no sooner had the clinician received this warning than the laboratory workers were given a caution. Pathologists have naturally long been keenly aware of the risks they run in handling highly infectious material,[10] and no medical school is complete without its awful example—and no mere legend—of a pathologist who pricked himself at a necropsy and died within 48 hours. A more subtle infectious hazard came to light last year when D. D. Reid,[11] of the London School of Hygiene and Tropical Medicine, reported that pathologists and laboratory technicians had in general a much higher incidence of disabling tuberculosis than comparable groups of other workers. Investigations[12,13] in laboratories where tuberculous material was handled showed that infectious particles sometimes escaped into the air when containers were centrifuged or their caps unscrewed.

A special working party with A. J. H. Tomlinson as chairman has now issued a report on the best precautions to take against the spread of tuberculous infection in diagnostic laboratories, animal houses, and post-mortem rooms.[14] The recommendations give detailed guidance on the design and handling of equipment, the construction of laboratories and other places of work, the supervision of technicians, and the care of experimental animals. The thorough and practical advice which the working party gives will probably be of great help to many pathologists. There seem to be no short-cuts: irradiation of the air with ultra-violet light, for instance, is considered unlikely to offer any useful protection. On the contrary, the need for uncommon personal care is evident throughout the report.

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[2] Rogers, N. C., Wilson, A. O., Meynell, M. J., and Cooke, W. T., *Lancet*, 1956, **2**, 651.
[3] Brockis, J. G., and Jones, E. T., *Brit. med. J.*, 1956, **2**, 1524.
[4] Stumpf, H. H., Wilens, S. L., and Somoza, C., *Lab. Invest.*, 1956, **5**, 224.
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[6] Carone, F. A., and Liebow, A. A., *New Engl. J. Med.*, 1957, **257**, 690.
[7] Baar, H. S., and Wolff, O. H., *Lancet*, 1957, **1**, 812.
[8] *Brit. med. J.*, 1956, **1**, 735.
[9] Doll, R., and Hill, A. B., *Brit. med. J.*, 1957, **1**, 372.
[10] Ibid., 1957, **2**, 35.
[11] Reid, D. D., ibid., 1957, **2**, 10.
[12] Tomlinson, A. J. H., ibid., 1957, **2**, 15.
[13] Whitwell, F., Taylor, P. J., and Oliver, A. J., *J. clin. Path.*, 1957, **10**, 88.
[14] Report to the Public Health Laboratory Service and to the Central Pathological Committee of a Special Working Party, *Monthly Bull. Minist. Hlth. Lab. Serv.*, 1958, **17**, 10.

SOME THOUGHTS ON MENTAL EFFECTS OF AMPUTATION

BY

R. LANGDALE KELHAM, O.B.E., F.R.C.S.

The occurrence of two great wars in the lifetime of many of us, together with the increasing industrialization and mechanization in this and other countries, has resulted in the loss of limbs by amputation to a greater extent than had ever been experienced before 1914. The moral responsibility for undertaking schemes for the rehabilitation of personnel from the Services was immediately recognized; later, such schemes were available to the industrially injured, and finally, under the National Health Service, to the whole community.

In the early days these schemes provided for the supply of artificial limbs, while the other aspects of rehabilitation of the amputee were dealt with largely in watertight compartments, there being little co-ordination between the various branches then operating. It is now recognized, and coming to be acted upon, that the success of rehabilitation depends upon closely correlated team-work. While that aspect of the work relating to the physical preparation of the patient now receives full consideration and much has been written upon it, it is questionable whether the same consideration is being given to the mental approach to the patient.

Dr. Allwood-Paredes, Director General of Health, El Salvador, writes in the *Chronicle of the World Health Organization* of July, 1956: "The present trend towards narrow specialization, the exaggerated emphasis on technology, and the overwhelming demands upon his services generally prevent the physician from paying sufficient attention to the patient's psychological needs."

All are now agreed that physical rehabilitation alone cannot make for complete rehabilitation, but very little has been published on the mental side of the subject, with the exception of a few reports from America, and the purpose of this article is to endeavour to relate some of the effects of amputation upon the mind of the patient and to give some indication of the means by which we can attempt to counteract adverse effects.

Shock

All amputations, whether they be predetermined following a long-standing illness or result from sudden trauma, produce in the sufferer a mental shock. In the former case the patient has time to think and brood over the loss of a limb which has become inevitable, and the thoughts which pass through his mind can well be imagined. What we cannot predict is how he will eventually react to the shock when amputation takes place. In the latter case we can well imagine the feelings of a person who, admitted to hospital following an accident, is taken to the operating theatre, and on return to bed and consciousness realizes that a limb is missing. In the former we can do something to brief the patient and prepare him for the future, but in the latter we cannot.

Types of Reactions

The impact of amputation upon the mind of the individual varies between patients, and both the short- and long-term effects and reactions thereto will be associated with the personality of the individual. Upon some there will be apparently no adverse effects, but there are always some upon whom the effects are such as to alter the course of their lives and have an adverse influence upon their temperament. It is concerning this latter group that the following remarks are made, it being better to be prepared to anticipate possible adverse effects than to have to deal with them too late.

Fears.—The loss of the limb usually first demonstrates itself in the form of depression, despondency, and hopelessness, and with these is found a fear of dependency upon others on account of the anticipated crippledom. Experience in dealing with very large numbers of amputees over the years makes it abundantly clear that this fear of dependency is very real. Next we have the fear, frequently unsubstantiated, that they will be forced to undertake some entirely different form of work, if able to undertake any, for which they have had no training. This leads to fears of economic catastrophe and the inability to maintain a home. Social and domestic apprehensions are by no means rare, and, unfortunately, have been substantiated in some cases in that the fact of amputation has resulted in the break-up of marriages and of engagements, the one or other partner being horrified at the idea of linking their lives to a cripple.

Defiance.—There are others, on the other hand, who in the early stages do not appear to have suffered any of the above fears, but rather exhibit a state of defiance and declare with emphasis that the loss of a limb will never "get them down." They are determined to overcome their disability and meet all setbacks with optimism. At the beginning they carry out their declared intentions, but one has come to regard them with suspicion because in a number of instances the defiance has proved to be unstable and, unless carefully followed up, they lose their determination and enthusiasm.

Acceptance.—Next we have a group, fortunately a large one, of those who accept and are resigned to the fact of amputation and are searching for some compensatory factor which will tend to balance their loss. These we can help, and they are the easiest of all amputees to deal with.

Aggression.—There are some who become aggressive and consider that they have been unfairly treated by society, against which they bear a grudge, and particularly against those who are trying to help them. They develop obsessions, and nothing will convince them that the chance ills and misfortune which may arise are not the direct result of amputation; the effects of such happenings are transferred to the stump or the artificial limb or both. In this group we find some who develop stump pains which are often untreatable, and, despite every known form of treatment having been tried without lasting success, they complain that nothing is done for them. Complaints against the limb are common in these cases, though no physical reason can be found to justify complaint. In a number of instances it has been proved that the real cause had nothing to do with the limb and had to be sought elsewhere.

Parents' Reactions.—Most parents of congenitally malformed children are very good with them, but some are not. Instances are known when the parents have neglected their child and are horrified at the sight of the deformity. Some husbands and wives have blamed one another for their child's deformity, and the domestic warfare which results has militated against the satisfactory rehabilitation of the child.

Reactions of Relatives of the Elderly Patient.—These relatives can be divided into three classes: (1) those who do everything possible to help and encourage the amputee to persevere with the limb, and enable him to become independent of outside help—the elderly person is just as anxious to gain independence as those of any other age; (2) those who, through misplaced sympathy, are always offering help which is not needed, and so undo all the good that has been done in the training schools and force the patient to feel that he is not so competent as he thought; and (3) those to whom the elderly amputee is a nuisance in the home; they make no effort to help and encourage, but neglect the patient as much as they can, the result being that the patient, realizing he is regarded as a nuisance, gives up hope, reverts to bed, and wants to get back to a bed in hospital, where he received attention, encouragement, and companionship.

Later Reactions

During the second world war an investigation was carried out into the mental reactions of several hundred Service men who had lost limbs in action and most of whom had been wearing artificial limbs for about a year. All the reactions previously referred to were observed, but one aspect of the matter became noticeable in that those who had made a Service life their career and were "regulars" suffered the effect of amputation much more than did those who had joined the Services as "hostilities only" men. The former realized that the loss of the limb had put an end to their chosen career in most cases, and they had not accepted that a compensatory career could be found. The latter, on the other hand, more readily accepted the disablement and tended to regard it as a "badge of honour" and evidence that they had served their country. It was interesting to note that these same men, as time went on and they had secured employment, were the most anxious to conceal their disability, and several proudly announced that "even my employer does not know that I have lost a limb." Such cases as these can be regarded as fully rehabilitated from every point of view.

Many civilians served during the war as air-raid wardens, and among them some women wardens suffered the loss of a limb during the bombing. On being supplied with artificial limbs they were determined to return to their posts as wardens, and did so, filled with the urge to continue serving their country. They were most successful arm- and leg-wearers.

When the war ended and there was nothing more they could do to help, a change became noticeable in their attitude to life and limb-wearing which indicated a deterioration of spirit. This change may well have been due to the fact that the end of the war was the first opportunity they had had for several years to think of what the loss of a limb really meant to their future, there being nothing to replace the excitement and enthusiasm which the war years provided. Some became aggressive and difficult to handle, others showed hysterical manifestations, and others just lost hope; these would now be regarded as instances of unstable defiance.

There are other amputees, quite an appreciable number, who appear to react well and accept the disability in its early stages and sometimes for a considerable time. They enter or re-enter employment and hold down their jobs with satisfaction to themselves and their employers perhaps for years; then suddenly a change takes place in their outlook and, more often, in their attitude to their artificial limbs, sometimes associated with the onset of stump pain for the first time; they cease to be apparently contented and rehabilitated persons.

When everything has been done to correct, if need be, any imperfection in the type or fit of the limb—though in these cases there is usually little to be corrected—it will be discovered after long probing that the real cause of the change that has taken place is far removed from the loss of limb, from the stump, or from the artificial limb. More often than not it lies in some domestic upheaval—divorce, desertion, or some social or tragic happening affecting a son or daughter of the patient. Occasionally the cause has been the failure of a business in which the patient had sunk his capital.

Patients are unwilling to talk about such matters, not realizing that they have any bearing upon their prosthetic troubles, and only by the expenditure of much time and a very good doctor-patient relationship can the facts be elicited. Even then the trouble may not be resolved, but the doctor or limb surgeon can put to the patient the right perspective regarding the stump and artificial limb in relation to the trouble.

Approach to the Patient

Methods of approach will no doubt have already suggested themselves from the foregoing, and there is every reason to believe that many of the fears to which the potential amputee or recently amputated person is liable can be allayed to a great extent by the right approach and action of those who will be dealing with the patient—that is, the rehabilitation team comprising the doctors, surgeons, nurses, physiotherapists, training instructors, welfare officers, and almoners, and the disablement resettlement officers.

To ensure the best results it is necessary that all these persons are conversant with the possible impact of amputation upon the mind of the patients and have a fair knowledge of the potentialities of an amputee when properly fitted and trained in the use of a limb. Without such knowledge they are not in the best position to provide the necessary stimulus and encouragement for the future. Cheerfulness and reasoned optimism are needed, carefully avoiding the holding out of extravagantly optimistic hopes such as telling elderly patients that artificial limbs are so marvellous now that they will be able to walk just as they did before amputation—hopes that turn to depression later on when these cannot be realized. The encouragement should, of course, be related to the level of amputation, the age, and the physical condition.

It is advisable to prepare patients for the fact that after amputation they will feel their feet or hands in a phantom form which will be a somewhat different sensation from that of normal feet or hands—they will become conscious of either a movement of the digits or a cramping sensation, or perhaps a tingling. In a few months they will become accustomed to these strange sensations or ignore them.

If such a warning is not given, the patient is apt to think, when these sensations develop, that something has gone wrong with the stump, and through worrying about it the perfectly normal sensation may progress into one of phantom pain.

Lower Extremity Amputations

Many amputees ask what they will look like when fitted with a limb, and will they appear normal. They can be assured, if leg amputees, that when sitting and standing they will appear quite normal, but that their gait when walking will depend on the level of amputation and on their co-operation in the training courses, and will vary between normal and, for higher-thigh amputations, a limp which may be no worse than that of a sufferer from a rheumatic hip. The more elderly will walk as if they had an ankylosed knee. A woman, unless she has had a Syme amputation, will not be discernible as an amputee at all when sitting or standing, since all artificial limbs are made to the exact dimensions of the natural limb. Women patients in particular lay great stress on this.

Employment.—All of wage-earning age can be found employment or be trained in new work if unable to return to the old. Provided the correct placement has been assessed and effected by those responsible, the loss of one leg does not necessarily imply a sedentary occupation or one of less remuneration or interest.

An investigation into the effect of amputation upon employment in which the records of 4,000 users were scrutinized showed that, of those amputated above the knee, 65% returned to the same or similar work, 13.5% became financially better off, 16.5% obtained less remuneration, and 5% were unemployed or under training at time of check. Among those who obtained less remuneration were undoubtedly some who had not reacted well to the loss, and some perhaps were given work more in accordance with their disability than with their ability. Of those amputated below the knee, 69.65% returned to the same work, 10.35% obtained higher remuneration, 15.25% received less remuneration, and 4.75% were unemployed or under treatment. It does not follow that an amputee, like other persons, necessarily desires to return to the same occupation after a break. Some take the opportunity of making a change. For instance, a lorry driver (below-knee amputation) became an engine driver, whilst an engine driver

became a lorry driver ; a milk-roundsman after amputation became a mechanic at a much higher wage.

Disablement Resettlement.—Welfare officers and others concerned with placement will advise on all these points. A leg amputee can in fact undertake any work which does not entail too much rapid or prolonged standing and movement, and many are fully engaged in agriculture and the building trade, for example. Elderly persons who have passed the normal working age often continue at work, and others change to more sedentary occupations. So far as elderly bilateral amputees are concerned, the majority can get about on short peg or rocker legs, and some progress to full-length articulated legs sufficiently well to become independent of assistance and can interest and occupy themselves in the home and garden.

Domestic.—Since the majority of leg amputees can be, and are, found employment, there should be no fears regarding the ability to maintain a home. The amputee's near relatives should be told that the loss of one leg should make no real difference to home life other than that in some instances activity may be reduced. In Canada, during and after the last war, an excellent system was in force whereby a representative of the War Amputees of Canada, himself a limbless man, visited the homes of returning Service men who had undergone amputation, and explained matters to the families and demonstrated the capabilities of those without a limb. This did much good because the relatives knew what to expect and how to treat them.

Social.—Sporting activities, other than the more strenuous field games and track events, can be resumed. Tennis, badminton, golf, shooting, riding, fishing, are commonly enjoyed by those wearing an artificial leg. When the favoured sport cannot be undertaken there are compensations to be found in taking up other activities. When dealing with elderly patients it is desirable to discuss the case with relatives with whom the patient will live, in order to avoid the risk of conditions arising such as have been mentioned. This is also the case when congenitally malformed children are being dealt with. The parents should be told that they are in no way responsible for the child's malformation. The children themselves should be allowed to develop normally —and they invariably do so develop if allowed—and should play games and mix with normal children. The fact that they tend to damage their artificial limbs should not be allowed to detract from their physical activities.

Upper Extremity Amputations

Broadly speaking, the loss of an arm creates a greater shock than does that of a leg. In the latter case the patient knows he will get about somehow, even if only on crutches, but the arm amputee often feels that all is lost, and to make the best of things will begin to rely upon the remaining hand and arm for everything. This makes the rehabilitation by an arm prosthesis much more difficult. By the time the stump is ready to be fitted with an arm the patient will have achieved a considerable degree of efficiency with the remaining hand and be proud of it, and the thought of an artificial arm being applied is rather a blow to his pride in achievement. The result is that the stump becomes dependent and inert, the shoulder is raised, and an abnormal appearance is developed.

The mental approach to an arm amputee is therefore somewhat different from that to a leg amputee. The latter, even without stump muscle re-education and other treatment, can be fitted and will walk, though badly, while the arm amputee who regards his stump as useless will make no use of an artificial arm.

The first approach, therefore, is to inculcate in the mind of the patient that the stump is of use. This cannot be achieved if nurses and others in attendance on the patient do everything for him, such as feeding, writing, etc., and so prevent him from acquiring a sense of independence beyond that which he can attain with one hand. In using the stump for every possible purpose he will be exercising the proximal joint and helping forward his physical preparation.

To use the stump a fork, spoon, pencil, or a loop of wire for holding a cigarette can be bandaged on to it ; better still, an adjustable gauntlet of leather or webbing with slots cut or loops sewn on can easily be made and can be used for above- or below-elbow stumps.

It is better that a right-handed person losing a right hand should write with the stump rather than learn to write with the left hand.

It is noticeable that those who have been treated in this manner in the early stages and before a limb is supplied are more willing to accept an arm and make better use of it than do those who have not been so treated.

From this point of view, bilateral arm amputees are quite a different proposition. These patients are always ready and most anxious to try out any method which will render them independent, and they become very efficient in a short time, using the gauntlets. To enable them to turn over the pages of a book, a pencil with a rubber on the end can be fitted into the gauntlet. These cases are the easiest of all arm amputees to rehabilitate, and their approach to their disability appears to be that of "give us the tools and we will do the job" ; it is therefore for us to devise the means to help them.

In the years during and immediately after the first world war artificial arms were not put to the same good use that they are to-day, and in fact many when supplied were rarely used at all. To-day, the fit, design, and function of arms have been greatly improved ; more attention is given to preparation of the patient, and training in the use of the arm is more intense. The prescription of the correct type of prosthesis and appliances, the training, and the provision of encouragement and example have enabled a high proportion of arm amputees to compete in the open labour market on equal terms with their sound fellow men. Patients should be informed of this, and be given the opportunity to see for themselves what a trained arm-wearer can do.

A scrutiny of the records of 1,000 cases showed the effect of arm amputation upon employment ; it was as follows. Of those amputated above the elbow, 48% returned to the same work, 32% obtained more remunerative work, and 20% obtained less remunerative work. Of those amputated below the elbow, 42% returned to the same occupation, 42% obtained more remunerative work, and 16% obtained less remunerative work.

The shock from loss of an arm being perhaps greater from loss of the leg, it is not surprising that the proportion of those who failed to make good is a little greater amongst arm amputees. Personality factors enter into this, and also the fact that arm-training is refused by some who have already been promised work by former employers—work which is often not of the same standard, through either sympathy or lack of understanding of the problem of the disabled.

In their own interest all arm amputees should be impressed with the importance of accepting the offer of arm-training.

Group Therapy.—Ever since the supply of artificial limbs to the war-disabled came to be regarded as a national responsibility, and subsequently, when that responsibility applied to all civilians who had lost limbs from any cause, group therapy has been practised, with a twofold advantage. First, in the treating of amputees in groups, whether for physical preparation, limb-fitting, or training, all those having similar disabilities discuss their problems with one another, observe the activities of those in a more advanced stage than themselves, and develop a spirit of competition and cheerfulness that is most beneficial to morale. The morale and functional efficiency of amputees who had been dealt with collectively were observed to be much higher than in amputees who, before the introduction of the National Health Service, obtained their limbs privately. Secondly, members of the staff of limb centres and of hospitals which specialize in the treatment of amputees become experienced in the specific requirements of amputees and in their handling from both the mental and the physical aspect.

Recent amputees should be enabled to visit limb centres and training schools whenever possible; it is good for morale, and when the time comes for them to be fitted with limbs they approach the matter with more enthusiasm and hope.

Films are available which depict the activities of arm- and leg-wearers who have been rehabilitated, and these films have been shown in hospitals and other institutions with beneficial results.

Summary

Attention is called to the impact of amputation upon the mind of the patient. The manner in which some patients react to the shock and the fears ever present in their minds is remarked upon. The long-term effects of amputation which may come to light after some years are noted. The importance of telling patients all that will happen to them and the reasons therefor, and what their future potentialities will be so far as can be assessed, is emphasized, and some indication of the method of approach best suited to their needs is given.

I thank Dr. J. B. Randell for his help in the preparation of this article, and the Chief Medical Officer, Ministry of Health, for permission to publish.

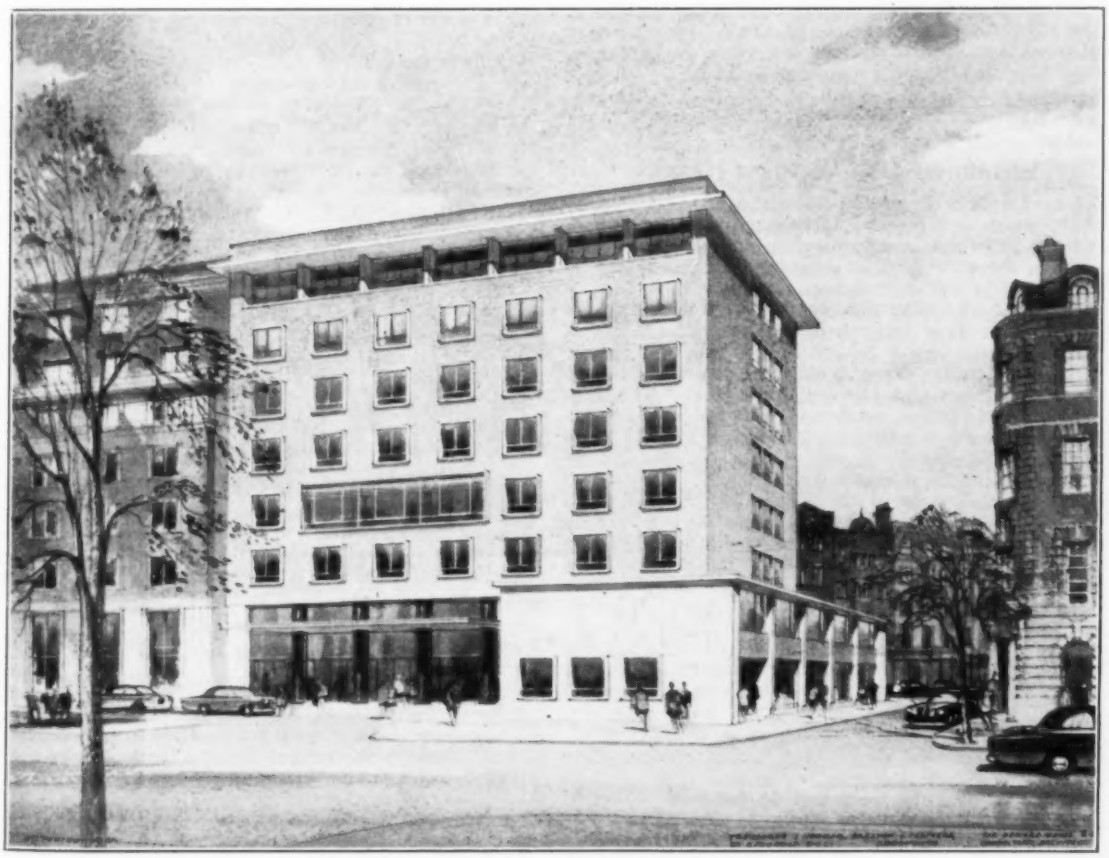
COLLEGE OF GENERAL PRACTITIONERS

PROPOSED NEW BUILDING IN LINCOLN'S INN FIELDS

The following statement has been issued by the College of General Practitioners:

Permission has been granted by the London County Council for the new headquarters of the College of General Practitioners to be built alongside the Royal College of Surgeons in Lincoln's Inn Fields. This close association of two medical colleges—the youngest and one of the oldest, possibly sharing some of each other's resources and both anxious about the future of general practice—should do boundless good to British medicine at this critical time. The architects are Trehearne & Norman, Preston & Partners; the consulting architect is Sir Edward Maufe, R.A.

The new building—a gift from an anonymous donor—will contain a conference hall, lecture theatre, library, museum, council chamber, committee rooms, and restaurant. An important feature will be the "equipment and premises" demonstration rooms where apparatus used by family doctors throughout the Commonwealth will be displayed, together with models and drawings of different types of premises. Other parts of the building will be allocated to undergraduate and postgraduate education, to the College's journal, and to its research headquarters, which will include a records unit and a statistical department; the latter may be of value, also, to the Imperial Cancer Research Laboratories near by. In addition to books, other publications, and archives, the library will preserve films and sound recordings of interest to general practitioners. Underground garage accommodation will be provided.



The future College of General Practitioners: an artist's impression.

Correspondence

Intraperitoneal Blood Transfusion

SIR,—I was very interested and delighted to read the paper by Dr. Lorna G. Macdougall (*Journal* January 18, p. 139) on intraperitoneal blood transfusions in children. In my view this procedure is far too little known, and because of its efficacy and simplicity I feel it should be much more widely appreciated and used.

It is, of course, not new; in fact, it was being extensively employed in Professor W. McKim Marriott's paediatric department in St. Louis, U.S.A., so long ago as 1923. I first became acquainted with it at that time, when I was working with him there, where it was used extensively; since then I have frequently advocated it. Those not familiar with the procedure in practice, nor acquainted with the literature on the subject and the experimental work which has been carried out, are apt to be sceptical, not only as to its efficacy, but as to whether it really is a true transfusion. In addition to the references quoted by Dr. Macdougall, I would like to mention the paper by David Levi.[1]

Quite recently in association with pathological colleagues at the London Hospital we have had the opportunity of confirming still further the fact that blood given in this way is a true transfusion. Cells labelled with radioactive chromium were injected into the peritoneal cavity of a child patient, and these cells subsequently appeared in the peripheral circulation. In another case, more significantly, a similar result was confirmed by the older Ashby technique (using cells of a different blood group from that of the patient). This procedure therefore is not only efficacious in practice but can be properly regarded as a true transfusion. The number of our observations of the kind just referred to is as yet insufficient to warrant publication in detail now, but I hope that this will be accomplished later.—I am, etc.,

London, E.1. K. H. TALLERMAN.

REFERENCE

[1] Levi, D., *Brit. J. exp. Path.*, 1927, **8**, 355.

Informal Admission of Mental Defectives

SIR,—I write as the medical officer of a large and, I like to think, progressive hospital for mental defectives, whose policy is to train as many patients as possible to take their place in the community as soon as their rehabilitation is complete. In this post I have frequently found myself caught in the cross-fire between the forces of the "Civil-Liberty" Guards on the one hand and those of the "Protect-the-Public-at-all-Costs" Brigade on the other. It is not surprising, therefore, that I should feel considerable concern at the publication of a Ministry of Health circular recommending the informal admission of mental defectives to mental deficiency hospitals (*Journal*, January 25, p. 212), and at the uncritical enthusiasm with which politicians and press have welcomed this allegedly great advance.

The modern concept of mental deficiency is that of social incapacity of such a degree as to render an individual in need of care, supervision, and control for his own protection or for the protection of others. Mental illness on the other hand, in almost all cases, occurs in individuals previously able to lead a fully independent existence. However, examination of the circular referred to suggests that the Ministry of Health regards the mental defective as more capable of self-care than the voluntary patient suffering from mental illness, in that he is to be allowed to leave hospital immediately (i.e., without the 72 hours' notice at present required of the voluntary patients in a mental hospital) should he not respond to persuasion from the medical officer to remain.

It is true that the more severely handicapped mental defective could be admitted informally provided that the medical officer of the hospital were given power to detain him for a prescribed period pending provision for alternative care, should this prove necessary, without the risk of allegations of wrongful detention being subsequently levelled. However, this would seem to offer no advantage over an extension to all grades of mental defectives of the present arrangements under which the parents of these patients may place them under hospital care and retain the right to withdraw them on giving notice, so long as they are able to provide a satisfactory home for them. On the other hand, the admission of the higher-grade patients to mental deficiency hospitals results from their failure in the outside world, and any successful rehabilitation and training—which is of necessity prolonged in most cases—will be impossible if they are to be allowed to leave hospital whenever they wish. It is unrealistic to believe that they will be sufficiently self-critical to appreciate their own shortcomings and the benefits to be derived from further stay in hospital, particularly if they are encouraged in their resolve by the outside influences I have mentioned. I believe that for these reasons detention orders will be necessary in a higher proportion of these cases than the circular would suggest. The new recommendation will, I believe, expose the medical officer to even more concentrated cross-fire, while removing the protection previously afforded him by powers designed to safeguard the interests of the patient and the general public. —I am, etc.,

Bristol, 8. W. A. HEATON-WARD.

SIR,—The authorized informal admission of mental defectives to hospital, and the recommended termination of compulsory powers over the patients already in mental deficiency hospitals (*Journal*, January 25, p. 212), are things which sound altogether admirable, yet one important fact seems to be forgotten. Mental defectives are mentally deficient. How far can they really appreciate their own need for hospital care?

The power of discharge from hospital, previously vested in the Board of Control for the most part, can now be virtually in the hands of the mentally deficient patient himself. If such a patient intends to leave hospital, it is doubtful whether attempts to dissuade him from so doing by the hospital authorities will often carry very much weight. He will leave, perhaps with nowhere to go and with no one to take an interest in him, and will survive as best he can until he becomes "subject to be dealt with" under the Mental Deficiency Acts. To so qualify, he must either be found in unhappy circumstances, or else he must commit some antisocial act. Either method of qualification may involve considerable human suffering. It is true that many patients in mental deficiency hospitals are "childlike and prepared to accept whatever arrangements are made for them," but I doubt whether these are greatly in the majority, and even they can wander outside the hospital grounds, when there will be no legal justification for apprehending them. Again, many patients abscond from hospital for quite trivial reasons. Nor can I agree that the number of cases in which difficulties will arise if compulsory powers are withdrawn would be small.

The steps now encouraged are but a foretaste of the implications of the recent Royal Commission on the Law Relating to Mental Illness and Mental Deficiency. If they are widely followed, perhaps their results will sound a warning bell. The old laws may not have been perfect, but at least they had the protection of the patient and of the general public well in mind.—I am, etc.,

Near Taunton. M. P. NELSON.

Scabies on the Increase?

SIR,—Going over the 1957 out-patient figures for the department of dermatology at the Bradford Royal Infirmary, I was struck by the marked increase in the incidence of scabies. I give you the figures for the past three years:

Year	Cases of Scabies
1955	21
1956	15
1957	57

Of the 57 cases in 1957 just over 19% were sent up with the diagnosis of "? scabies"; over 80% were sent up undiagnosed or with various other diagnoses. Unless scabies produces the classical textbook picture it can be very deceiving. Therefore it may not be inappropriate to suggest that all cases of urticaria, and all cases of puzzling eruptions with marked nocturnal exacerbation of itching, should be considered with the view to eliminating scabies as the first step in differential diagnosis.—I am, etc.,

Bradford, 8. ALLAN BIGHAM.

Post-operative Position

SIR,—I hope that my old friend, Dr. H. L. Marriott, will not mind my disagreement with him on some of the points raised in his interesting and stimulating letter on post-operative posture (*Journal*, January 25, p. 215). We are on common ground inasmuch as we have both undergone a cholecystectomy, but, whereas I have anaesthetized Dr. Marriott, he has, as yet, not reciprocated this procedure!

Surgeons and anaesthetists are constantly striving to obtain an optimum post-operative posture after upper abdominal operations uncomplicated by thoracotomy, and Fowler's position still holds sway. Nature's pain-defence mechanism is minimal diaphragmatic excursion, but, unfortunately for the patient, productive cough is dependent far more on diaphragmatic than on intercostal movement. Fig. A in Dr. Marriott's letter suggests that diaphragmatic excursion will be reduced rather than—as is desirable—increased.

Two years ago I suggested nursing patients flat (with, of course, frequent changes from side to side) after gastrectomy in an attempt to overcome the gravitational disadvantage of achieving a productive cough in an upright posture. It was surprisingly ineffectual, and after a dozen cases had been so treated Fowler's position was readopted. With regard to stretching of the wound, which Dr. Marriott suggests is a disadvantage of Fowler's position, it seems to me that, if a patient with a vertical upper abdominal incision adopts the posture recommended by Dr. Marriott, it will be likely to prolong that uncomfortable transitory period during convalescence when one has the feeling that one will be permanently bent and unable to stand quite upright again.—I am, etc.,

London, W.C.2. H. K. ASHWORTH.

First Tuberculosis Dispensary

SIR,—The memorial lecture on Sir Robert Philip delivered by Dr. C. Clayson (*Journal*, December 28, 1957, p. 1503), and your accompanying annotation (p. 1534), repeat a traditional belief that the tuberculosis dispensary established by Philip in Edinburgh in 1887 was the first ever. The annual report 1956–7 of the National Association for the Prevention of Tuberculosis illustrates inside its front cover the premises, 20, Talbot Road, Paddington, described as "the first tuberculosis dispensary in London," established there in January, 1909.

We are concerned to question the correctness of these assertions and to press a claim to priority for the Liverpool Street Dispensary which was opened on June 13, 1848, in a large house at 6, Liverpool Street, in the City of London. The first annual report of this dispensary for the year 1848 records that "several gentlemen had prominently brought under their notice the great frequency and fatality of Diseases of the Chest among the indigent portion of the population and the unavoidably imperfect provision for their treatment in the Northern and Eastern Districts of the Metropolis. A meeting was accordingly held at the London Tavern on the 13th March at which a subcommittee was appointed to mature a plan . . . to maintain a Public Dispensary at which persons suffering from Affections of the Chest might receive gratuitous advice and medicine." Its first consulting physician was Dr. B. G. Babington—a Guy's Hospital physician and an active member of the management committee of the "Infirmary for Asthma, Consumption and Other Pulmonary Diseases" in Bishopsgate. This was almost 40 years before the publication of Koch's discovery of the tubercle bacillus and Sir Robert Philip's Edinburgh venture. In the first six months of its activities the Liverpool Street Dispensary accepted and treated 2,355 chest cases. Thereafter patients came at the rate of a hundred a day. This dispensary was the first stage of the expressed threefold intention of its founders to combat tuberculosis in the City and East London. The other two services which followed were the "City of London Hospital for Diseases of the Chest," opened in 1855 at the same premises it still occupies near Victoria Park, and a country sanatorium. The dispensary moved to the hospital premises in 1855 and its activities have continued there to this day in the out-patient department. Forty years later Sir Robert Philip adapted this scheme to the needs of Edinburgh, retaining the pattern of a threefold service in the form of his Victoria Dispensary, the Royal Victoria Hospital, Edinburgh, and a tuberculosis "colony."

That the preventive services provided by the Liverpool Street Dispensary may not have been as extensive as those of its much later counterparts in London, and that the premises were intended for temporary occupation until something better could be built later, seem to us in no way to invalidate the claim we make that by its independent existence and specialized activities from 1848 to 1855 it was the primogenitor of London's tuberculosis dispensaries.—We are, etc.,

London, S.E.1. W. HARTSTON.
London, E.2. W. F. WHEELER.

Rheumatic Fever Prophylaxis

SIR,—I would like to draw attention to a statement in your leader on the prophylaxis of rheumatic fever (*Journal*, January 4, p. 30). The Rheumatic Fever Committee of the Royal College of Physicians is quoted as suggesting oral penicillin or, as an alternative, "monthly intramuscular injection of 1.5 mega units (5 ml.) of benzathine penicillin." The leader then states that Markowitz and his colleagues,[1] "who used 600,000 units of penicillin G," have cast doubt on the effective prophylaxis of a single injection and that protection may be afforded for a short time only against infection with a virulent streptococcus.

In fact Markowitz and his colleagues, in the work referred to, found no infections with streptococci or recurrences of rheumatic fever in their series of patients treated with 1.2 mega units of benzathine penicillin G monthly, and it is only in their discussion that they question the efficacy of this form of treatment by quoting Stollerman and Rusoff,[2] whom, they state, found no penicillin levels in a third of patients at the end of four weeks. There is another report of the work by Markowitz[3] which was not specifically referred to. This dealt with the actual treatment of streptococcal infections in a closed community, and only 600,000 units of benzathine penicillin were given intramuscularly. As this is half of the recommended dose and was in an abnormal environment, it is hardly relevant to the present discussion.

Stollerman and Rusoff[2] found no estimable penicillin levels in a third of patients receiving 1.2 mega units, but these patients were actually getting two injections of 600,000 units, one in each buttock. It has been shown by Welch *et al.*[4] that injections of benzathine penicillin give a local deposit from which slow release gives long-lasting blood levels. An increase in amount of a single injection will not cause appreciably higher serum concentrations but will produce those concentrations for a longer period. Thus patients receiving 300,000 units in one injection had an average serum level of 0.047 unit per ml. at six days, while those receiving 600,000 units in one injection had average levels of 0.050 units per ml. at six days. The former, however, had positive blood samples in over 80% of cases for eight days, while the latter had them for 12 to 17 days. It can be seen, therefore, that if two separate local intramuscular deposits are set up they will give protection for only the number of days afforded by each individual dose, although the levels should be additive and thus higher for that period.

In fact there is extremely strong evidence of the efficacy of monthly injections of benzathine penicillin in preventing recurrences of rheumatic fever. The references confirming this statement are far too numerous to be quoted in their entirety, but I might mention a two-year follow-up of children who had had rheumatic fever.[5] In roughly 190 patient/years there were nine recurrences with oral penicillin, four recurrences with sulphadiazine, and no recurrences with benzathine penicillin 1.2 mega units in 2 ml. intramuscularly every four weeks. C. M. McCue *et al.*[6] review 5,289 patient/months on benzathine penicillin prophylaxis and found one single recurrence. They comment on the advantage of this form of treatment. The report of the World Health Organization on the Prevention of Rheumatic Fever[7] states that "prophylaxis with penicillin by mouth (100,000–200,000 units of benzyl penicillin twice a day) or by injections (1,200,000 units of benzathine penicillin intramuscularly once a month) has proved somewhat more effective than prophylaxis with sulphonamides. Oral penicillin has the advantage of ease of administration but, as in the case with sulphonamide drugs, has the disadvantage of requiring careful supervision to be sure of continuous prophylaxis. It is also expensive. Intramuscular benzathine penicillin assures continuous protection and is less expensive but has the disadvantage of requiring repeated injections, which are painful and which may be followed by local or general reactions."

It would seem, therefore, that the leader in question might mislead readers as to the generally accepted methods of preventing recurrences of rheumatic fever.—I am, etc.,

London, N.W.1. B. W. CROMIE.
Medical Adviser,
John Wyeth and Brother Ltd.

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Fluorescent Clothes

SIR,—Suggestions have reached us as to the effect that fluorescent items of clothing, such as socks, pullovers, and slacks, which are currently worn extensively by teenagers, might contain some radioactive material. If these articles of clothing were luminescent then there would be a strong possibility that they contained radioactive material. In fact, these items of clothing do not glow in the dark and this renders such a possibility highly unlikely.

Tests carried out by placing a typical sock of this type adjacent to a photographic emulsion showed no evidence of activity. This conclusion was confirmed by the use of sensitive counters which revealed no β or γ contamination above natural background levels and also no detectable α activity. These tests would appear to indicate that there is no hazard for radioactivity associated with the wearing of fluorescent clothing.

We are grateful to Dr. N. Miller, of the department of natural philosophy (physics), Edinburgh University, for his assistance, and to Professor J. H. F. Brotherston for permission to publish this note.

—We are, etc., A. R. MILLS.
Edinburgh, 8. R. STEELE.

Influenzal Bronchopneumonia

SIR,—There have been a large number of cases of influenzal bronchopneumonia in this area, and the frequency of different bacteria isolated from sputa may be of interest. I have personally scrutinized all case-notes and the cases have been classified as bronchopneumonia or bronchitis according to the radiologist's report. Only cases from which sputum was sent for examination and in which pathogens were isolated are included; cases with associated diseases, e.g., bronchiectasis, coronary disease, etc., have not been included. I made the post-mortem examination on most of the fatal cases and took swabs from the bronchi and lungs. The series is, as yet, incomplete because there are still patients in hospital whose notes I have not examined.

TABLE I.—*Children*

Type of Case	No.	Pathogens	Sensitivity to Antibiotics*	Remarks†
Fatal Cases				
Influenzal bronchopneumonia	3	*Staph. aureus*	All	Ages 14, 15, and 17
	2	,, ,,	C and E	Ages 8 and 14
	1	*Proteus* and paracolon	C and T	Age 13
Surviving Cases				
Influenzal bronchopneumonia	2	*Staph. aureus*	All	Evidence of influenza virus A in one.
Influenzal bronchitis	2	,, ,,	,,	

* Sensitivity to antibiotics: P—penicillin; E—erythromycin; C—chloramphenicol; T—tetracycline; S—streptomycin; All—sensitive to all five antibiotics.
† Blood was not sent from all patients for tests for influenza virus infection. All the specimens sent were positive.

It will be noted from Table I that in the children the commonest age of death was about 14 years, and that in 5 out of the 6 fatal cases the pathogenic organism was *Staphylococcus aureus*. It was also the only organism in the four cases of bronchopneumonia and bronchitis in children. It was therefore the predominant organism in children.

In adults (Table II) *Staphylococcus aureus* was not so common, and could be incriminated in only 4 of the 10 deaths. It was found in 19 out of 34 cases of bronchopneumonia and in 5 out of 10 cases of bronchitis. On the

TABLE II.—*Adults*

Type of Case	No.	Pathogens	Sensitivity to Antibiotics*	Remarks†
Fatal Cases				
Influenzal bronchopneumonia	2	*Staph. aureus*	All	Age 56–83
	1	,, ,,	C and E	
	1	,, ,,	All	
		Coliform and *Cl. Welchii*	C and T	
	2	Coliform	C, E, P, and T	
	3	*Proteus*	S, C, and T	
			1 S and C	
			2 resistant to S, C, and T	
	1	*Strep. pneumoniae*		
Surviving Cases				
Influenzal bronchopneumonia	13	*Staph. aureus*	All	Evidence of influenza virus A in two
	6	,, ,,	C and E	
	5	*Strep. pneumoniae*		Evidence of influenza virus A in three
	1	*Strep. pyogenes*		
	2	*Proteus*	C	
	1	Coliform and *H. influenzae*	S, C, and T	
	4	Coliform	S, C, and T	
	2	*H. influenzae*	S, C, and T	
Influenzal bronchitis	4	*Staph. aureus*	All	
	1	,, ,,	C, E, S, and T	
	5	Coliform	S, C, and T	Virus A present in one
Influenza only	2	*Staph. aureus*	All	
	1	Coliform	S, C, and T	
	1	*Strep. pneumoniae*		Virus A present
	1	*Staph. aureus* and *H. influenzae*	All S, C, and T	

*† See footnotes to Table I.

whole it did not seem to make any significant difference to the severity of the illness if the staphylococcus was resistant to penicillin and other antibiotics. *Haemophilus influenzae* evidently played only a minor role. In the four cases in which it was isolated, it was found with another organism twice.—I am, etc.,

Cottingham, E. Yorks. J. GORDON ALEXANDER.

Research Workers and Pre-registration Year

SIR,—It is pleasing to read the letter by Professor L. J. Witts (*Journal*, January 25, p. 222) advocating that a period of teaching and research should count as pre-registration experience. As long ago as 1952 I made this suggestion in a letter to the *Journal* (September 13, 1952, p. 615), and I

would like to make a few more points. Professor Witts neglects to mention an important situation, not nowadays obvious, which caused much anxiety at the time when the Medical Act of 1950 became law. Many of the men and women to whom he refers committed themselves to lengthy periods of study for combined degrees in science and medicine before the 1950 Act received its first reading. Thus a year of pre-registration experience was added to an already long course by legislation which could not reasonably have been expected at the time study began. This situation applied equally to those studying medicine alone, but here the hardship was felt most among another minority —namely, the married, the ex-Service, and those urgently needed in a family practice.

Professor Witts's suggestion that accredited teaching or research posts should count as pre-registration experience seems sound. It is supported by the fact that "medicine" or "surgery" in practice can mean "psychiatry" or "ophthalmology" respectively; hence the argument that the purpose of the 1950 Act is to produce better "basic doctors" falls down. The exclusion of research and teaching experience from acceptable pre-registration posts merely denotes that a poorly represented minority has once more been hit. In this respect it is interesting to reflect upon the inevitable indignation of the majority had a period of research experience been regarded as a *sine qua non* of full registration.

It is of interest to note that the pre-registration year makes a relevant contribution to the N.H.S. clinician's seniority, while little attention is paid to it among candidates for academic positions. Thus during the pre-registration year the future research worker is uprooted from the literature of his subject and loses contact with his university department and his former colleagues. This is aggravated by the absence of any remuneration for relevant extra qualifications, so that not even monetary compensation is made for the disrupting effect of pre-registration appointments on what must be regarded as the foundations of an academic or research career. It would therefore seem that the clinically inclined graduate has much to gain and his scientifically inclined colleague much to lose at present; and the sooner a fairer system is instituted, the better for all concerned.—I am, etc.,

Glasgow, W.2. STEWART FLETCHER.

Hypoglycaemia and the Mind

SIR,—Your leader on this subject is timely (*Journal*, January 18, p. 150). Undoubtedly functional hypoglycaemia is commoner than is suspected; the reason why it is not more frequently diagnosed is that it is seldom possible to do blood-sugar estimations at the time of occurrence of the symptoms, which, as in most functional disorders, are transient. Nevertheless, glucose in tablet and parenteral form can be carried in every medical bag: if from the history of poor diet it seems likely that hypoglycaemia is present there is a rapid improvement in symptoms after glucose administration.

In the course of seeing patients with headache, it is not uncommon to see cases of hypoglycaemic headache, either simple or acting as precipitants of tension headaches or true migraine. Some cases of very severe migraine are precipitated by hypoglycaemia, and the attacks are reduced in severity and number with simple dietary measures such as a high protein, low carbohydrate diet. Attempts at studying these cases with glucose tolerance curves have given results difficult to interpret, but in general two classes are found: one in which the curves are low and flat; and another in which there is a rapid rise of the blood-sugar level followed by a rapid fall, symptoms occurring during the rapid fall in blood-sugar level. The low, flat curves have been found in cases of fatigue and also associated with premenstrual tension.

It is highly probable that functional hypoglycaemia accounts for some road accidents. One of my patients presented himself with typical functional hypoglycaemic headaches, and did well on simple dietary measures. Three years later he came again in great distress, having had his driving licence taken away by the police (very properly), having had what the policeman diagnosed as an epileptic fit by the side of his car. He had driven for many hours throughout the night on his way to his holiday resort, and had only attempted to eat one sandwich, which was rejected as it was bad. An E.E.G. was done and reported on by Dr. E. Jacoby as being normal except for some theta activity when the test was done after fasting and the blood sugar was 50 mg.%.

Among other patients, I can recall reviving an unconscious patient with glucose in a ladies' hairdressing establishment. She subsequently said that she was fasting for the sake of her figure. In her case too she had had a long journey the previous day.

A boy of 12 was prone to attacks of violence and destructiveness. A careful record of the times of his outbursts suggested that he might be getting functional hypoglycaemia. With him dietary measures had a good effect, and only recently the mother said how well he had done since this simple treatment was begun.

Finally, I think that the prevalent habit of going to work without breakfast is the cause of a good deal of the fainting at work and in the office in the middle of the morning, especially in young girls. The motto must be "Eat and be sweet-tempered," especially before driving long distances.—I am, etc.,

Birmingham, 27. K. M. HAY.

Unusual Transmission of the Haemophilic Gene

SIR,—Since the publication of our article on this subject (*Journal*, December 28, 1957, p. 1528), patient Mrs. E. R. (V 4) has been delivered of a male child (S. R.) whose blood we have found to be deficient in anti-haemophilic globulin. The mother received one pint (0.6 l.) of fresh blood at the onset of the first stage of labour; no abnormal bleeding was encountered before, during, or after the birth of the baby, who weighed 8 lb. 5 oz. (3.8 kg.). That this boy is a haemophiliac is still in conformity with the usual recessive sex-linked character, but this does not favour or rule out any of the possible explanations we have offered for the occurrence of this disease in his sister and female cousin.—We are, etc.,

JOHN F. WILKINSON. F. NOUR-ELDIN.
Manchester, 13. M. C. G. ISRAËLS. R. L. TURNER.

Early Separation of Handicapped Children from Parents

SIR,—Mrs. B. I. Ingall (*Journal*, December 28, 1957, p. 1545) is indignant at my suggestion that deaf children should not go away to school at an early age. It is impossible not to generalize, as I was thinking of all handicapped children. Undoubtedly there are some cases where it will be essential for the child to be removed from home, but weekly boarding would be preferable to termly boarding, and where possible local transport or a peripatetic teacher should be used.—I am, etc.,

White Colne, Essex. J. VINCENZI.

Anxious Patient and Worried Doctor

SIR,—I have followed with interest the correspondence (*Journal*, January 4, p. 40) following on your annotation (*Journal*, December 21, 1957, p. 1483) under the above title, and I have wondered how often "cancer apprehension" is considered as a differential diagnosis to neurosis, hypochondriasis, etc. Patients suffering from "cancer apprehension" go to their family doctor complaining of some ill-defined symptoms. When they are given a bottle of medicine they are *not* reassured, and return "to live on the doctor's doorstep."

During a long experience in the out-patients department of my hospital, I saw very many such cases, and the principle I adopted was, after careful examination, to state, "I am glad to say that there is nothing serious and no evidence of cancer," taking care to emphasize the word cancer. On a great many occasions the patients have replied in some such words as, "Thank God, that was what was really worrying me." Some of these patients are brave enough to mention the word cancer to their doctor, and he, with the best of intentions, tries to "laugh it out of them." The

result is that the patient feels a fool, never mentions the word again, but goes on worrying. On several occasions at the end of a lecture to the laity—I gave 74 such lectures in this area during 1957—a member of the audience has got up and said, "It is all very well your advising us to go to the doctor if certain symptoms are present, but I could not speak to my doctor about cancer—I hate being laughed at."

I do not suggest that there is a large percentage of neurotics who are "cancer apprehensives," but it is worth while to try to find out.—I am, etc.,

Oxford. MALCOLM DONALDSON.

Chlorpromazine Jaundice

SIR,—Drs. S. Benaim and A. J. Coppen (*Journal*, January 4, p. 41) mention that failure to remember that chlorpromazine jaundice may develop after the drug has been stopped has resulted in patients being subjected to unnecessary operations. The estimation of the serum glutamic-oxalacetic transaminase carried out early in the attack of jaundice should prevent this mistake. In toxic jaundice such as caused by chlorpromazine and in infective hepatitis the serum GO-transaminase level is greatly increased. There is a close correlation between the liver damage and the enzyme level in the serum.[1]

A man of 70 was recently seen who after chlorpromazine developed jaundice: the serum GO-transaminase was found to be 56,000 units % (normal 800–4,000 units %). Ten days later, when the jaundice was fading and the patient's general condition improving, the serum GO-transaminase was 3,500 units %.

Serum GO-transaminase estimation may prove to be a most useful laboratory method in the differential diagnosis of jaundice. May I suggest that it would be better to follow the established custom in biochemistry and give figures per cent. rather than per ml., as has been done in overseas literature?—I am, etc.,

Worthing, Sussex. R. AIDIN.

REFERENCE

[1] LaDue, J. S., and Wroblewski, F., Exhibit at American Medical Association Convention, Atlantic City, 1955.

Drug Firm Representatives

SIR,—Many practitioners will doubtless want to join in the protest against the number of representatives of drug firms who call upon them to explain the superiority of their wares over others. Although these persuasive salesmen are in no way to blame and are generally most courteous, the army of those so employed, the quantities of elegantly packed free samples which they bring or which are sent to us by post, accompanied by expensively got up literature and, not infrequently, by little plastic gifts for the practitioner—all these things must inevitably add to the cost of the preparations being thus advertised to the profession. Surely some unified and more objective way could be found of introducing new pharmaceutical products to the attention of hospitals and practitioners without thus unnecessarily increasing their costs.

What the high price of many modern preparations implies for doctors and patients in those territories where there is much less money available for the health services than here may well have been brought home to us on reading Dr. Joseph Luder's most interesting article in the *Journal* of November 16, 1957 (p. 1143), on "Some Paediatric Problems of Uganda," where, he tells us, there is a shortage of all drugs.—I am, etc.,

London, S.E.17. YOLANDE M. FRIEDL.

Five Years of General Practice

SIR,—I have been interested in the correspondence in the *Journal* about psychoneurotics in general practice. I was taught that psychoneurosis means the exaggerated, bizarre, or inappropriate reaction to stress, which may or may not include a somatic manifestation.

I work in a country area where most patients are resilient and self-reliant. I have no statistics to support me, but my impression is that the incidence of psychoneurosis here is less than the figures which have recently been quoted; less than Dr. John Fry's 8.5% (*Journal*, December 21, 1957, p. 1453). We all have problems to face; people used to go to the parson, now more frequently they go to the doctor. Many consult me on purely private matters in this uncertain age of financial hardship and housing shortage and all the train of personal problems and sometimes tragedy that arises therefrom. Perhaps Dr. Alfred Model's patient (*Journal*, January 11, p. 101) just wanted to discuss his problem with a disinterested third party. Is he therefore to be labelled a psychoneurotic?

My experience is that where a patient consults me with a complaint of specific bodily ailment, if I look far enough I usually find an organic cause; if I fail to do so, time usually proves that I have not been a sufficiently astute diagnostician. A very small minority prove to have been psychoneurotic in cause; in a relatively closed community like this there is little chance of one's mistakes having moved out of the practice before they are revealed to one humiliatingly. If I asked every patient who came into the surgery whether they had any personal problems, I am sure all of them would confess to have some; remarkable must the few people be who have not. We can seldom mend an unhappy marriage, but we can, if we are alert, spot an early carcinoma of the stomach.—I am, etc.,

Wellesbourne, Warwick. LAWRENCE MACKIE.

Dislocation of Jaw

SIR,—Mr. G. Ellenbogen (*Journal*, January 11, p. 102) refers to a possible hazard to the thumbs of the operator when dislocations of the jaw are reduced by the standard method. I submit that it is usually unnecessary to introduce one's thumbs into the patient's mouth for this purpose, and that the manipulation is more expeditiously performed as follows: The patient lies supine and the surgeon stands at the head of the table. From this position it is easy to exert the necessary downwards and backwards pressure on the posterior end of the body of the mandible by applying the thumbs externally on the cheek, whilst at the same time elevating the chin with the fingers in the usual way. This is simpler and more pleasant for the surgeon and patient than the standard method, and in my limited experience has not failed.—I am, etc.,

Manchester, 4. J. P. LYTHGOE.

Weight in Relation to Pregnancy Toxaemia

SIR,—The apparent divergence of view expressed by Dr. E. C. Wood (*Journal*, December 21, 1957, p. 1493) and Dr. Cicely Williams (*Journal*, December 7, 1957, p. 1338) can be reconciled if the implications of their arguments are correctly appreciated. Dr. Williams has importantly drawn attention to the predisposing factor of obesity in the aetiology of pre-eclampsia. She has underlined the experimental fact of the association of renal changes with obesity and the clinical finding that the obese are conditioned to develop essential hypertension. She proceeds to say that "not all cases of pre-eclamptic toxaemia are associated with excess weight or weight gain" and also that "some women" (presumably toxaemic) "are badly or inadequately fed and are in need of extra nourishment." The natural inference from these statements is that diet must be relegated to the position of being merely another contributory factor in the aetiology. Further she states that the weight gain in pregnancy is due to obesity and to *increased fluid retention*, and directs treatment towards both by restricting sodium and the caloric intake and eventually rest—the treatment being not instituted unless the patient is 30% overweight, hypertensive, or oedematous. The indications appear to emphasize recognition of the disordered renal state towards which it is directed, rather than the obesity which had originally contributed to it.

It is to this increased rest coupled with sodium restriction that Dr. Wood ascribes the value of the treatment Dr. Williams advocates. He may be even correct in suspecting a mental influence in the toxaemic aetiology, for Lüvgren[1] has shown in the experimental animal that states of extreme

anxiety impose on the kidney a cortical ischaemia—a renal change for which there is both direct and indirect proof in pre-eclampsia.[2–6] Psychosomatic disorders, where a plausible transfer of the appetite centre to the cortex—with its implicit consequent voraciousness—as a result of emotional shock, may well explain certain cases of obesity, but hardly pre-eclampsia, for which Dr. Wood advances them as a cause. There is no evidence I am aware of that successfully supports the contention that toxaemia of pregnancy is an endocrinal disorder. Dr. Wood does, however, correctly contend that weight restriction in itself is not the specific prophylactic. The reduced circulation of the renal cortex is the immediate physio-pathological change responsible for the signs of pre-eclampsia, and for this the utero-renal reflex is in turn responsible. Treatment apparently directed towards obesity, or to an alleged dietetic aetiological factor, can be shown to owe its value almost entirely to its beneficial influence on the ischaemic pattern of the renal circulation, whose duality—difficult to uncover—Trueta[6] and Pappenheimer[7] have importantly explained.—I am, etc.,

London, W.1. JOHN SOPHIAN.

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6 Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L., *Studies of the Renal Circulation*, 1947. Blackwell, Oxford.
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Postmaturity

SIR,—Recent controversy on the prevention and treatment of postmaturity prompts me to draw attention to a new and potent source of error in the quest for that elusive date, the first day of the last menstrual period. The Maternity Services, in their wisdom, distribute a portion of their largesse when a pregnancy has reached the 28th week. Thrifty expectant mothers, mindful of the ever-diminishing purchasing power of the pound, not infrequently advance the date of their last period by a month or more in order to qualify for this money sooner. Feasts and holidays, such as Christmas, St. Patrick's Day, or the Twelfth of July, may be conveniently financed by this simple device. In consequence, honest medical attendants may be led into inducing these cases for postmaturity when, in fact, they may not even be at term. Indeed, some of these "postmature" infants have, on occasion, had to be popped hurriedly into premature infants' nurseries.

I am a firm believer in the prevention of foetal loss through postmaturity by timely induction of labour. The difficulty lies in selecting the cases requiring interference, and many factors have to be taken into consideration. These should be assessed with meticulous care by an experienced obstetrician, and each case considered on its merits. Until a reliable method is devised of estimating placental reserve antenatally, this seems to be the best way of reducing the toll of infant life from postmaturity, and yet avoiding unnecessary inductions as far as possible.—I am, etc.,

Omagh, Co. Tyrone, Northern Ireland. J. H. PATTERSON.

Storage of Vaccines

SIR,—With the introduction of anti-polio vaccination a new problem has arisen in general practice, in particular for those practising from lock-up surgeries, away from their residence. As the vaccine has to be stored in a refrigerator, I can safely presume there will be very few surgeries in which one of these could be found. I thought it would be worth while recording my way of overcoming this difficulty. I place a vacuum flask such as a "thermos" into my refrigerator at home, where I also keep the vaccines, and when the vaccines come out of the refrigerator they are put straight into the vacuum flask, and I take it down to the surgery and use it at the appointed time. Is there a better method?—I am, etc.,

Dartford, Kent. E. GANCZ.

Anaesthetic Hazard

SIR,—May I, through the medium of your columns, draw the attention of anaesthetists to what I consider to be a source of great danger arising out of the design of the latest model of the Boyle anaesthetic machine? In this latest model, in order to incorporate a safety device whereby trichlorethylene cannot be administered while the closed circuit is in use, the order of the ether and trichlorethylene bottles, which are in series, has been reversed so that the trichlorethylene bottle is now placed last in series. As a result of the adoption of this order the administration of both ether and trichlorethylene simultaneously results in ether vapour passing through the trichlorethylene bottle, with the inevitable consequence that the trichlorethylene becomes contaminated with ether and the contents of the trichlorethylene bottle are no longer safe for use in the production of an anaesthetic free from the hazard of fire or explosion.

To prove the existence of this hazard I recently conducted a short operating list under nitrous oxide, oxygen, ether, and trichlorethylene. Before commencing the list I dipped a gauze swab in the trichlorethylene and applied to it a lighted match; this produced only a dense volume of acrid black smoke. A similar test applied after the list was completed resulted in the gauze immediately bursting into flame. During the administration of the anaesthetics no more than half the ether-laden gases were passed over the surface of the trichlorethylene, with the lower edge of the plunger a good inch (2.5 cm.) above the surface of the trichlorethylene. At no time were the gases bubbled through the trichlorethylene.

It is clear that, if this danger is not removed, one or more disasters will occur. I would suggest that all machines of this type be immediately modified, and that in future, if the safety trichlorethylene device is to be retained, the ether and trichlorethylene bottles be coupled in parallel.—I am, etc.,

Bournemouth. S. F. DURRANS.

Surfeit of Medical Papers

SIR,—Dr. A. L. Goodall, in his recent letter (*Journal*, February 1, p. 283), emphasizes the real difficulties caused by the spate of modern medical publications. An excellent solution has been found, though it is not as widely known as it deserves to be.

An experienced editorial staff (including two medically qualified whole-timers) survey every month the entire output of over 1,600 of the world's leading journals. They endeavour to extract all significant papers, and submit these to appropriate experts (having a panel of over 400 specialists available). A signed abstract is prepared, presenting in brief the essence of the original, with expert comment if desirable. The output is published monthly as *Abstracts of World Medicine*, advertised in the medical press, and to be convinced of its value one need only send for a specimen copy. Incidentally, *Abstracts of World Medicine* is well indexed, and the very readable papers are grouped in logical families, so that collected back numbers become a pocket-library covering all fields (except specialized surgery) to within three to six months of current publications.—I am, etc.,

Paignton, Devon. J. F. BURDON.

Chest Radiography and Press Publicity

SIR,—A patient notified as suffering from pulmonary tuberculosis in 1956, who has been receiving chemotherapy for the past 12 months, and during this period has been screened once and *x*-rayed on four occasions, has written as follows:

"I am in the best of health and wish to thank you very much for your past help, but I now feel that, in view of the reports in the papers on the danger of *x*-rays, I wish to discontinue the treatment."

No doubt this is an isolated incident, but the decision of one patient may become the decision of many patients. In view of the publicity being given to the danger of radiation, is it not time that an authoritative statement was made regarding the hazards of chest radiography?—I am, etc.,

Rochester, Kent. H. J. ROBINSON.

Evidence from Bones

SIR,—I read the article by Dr. J. A. Imrie and Professor G. M. Wyburn (*Journal*, January 18, p. 128) with great interest and enjoyment, and would like to add further support to their estimate of the skeletal maturity of the bones. To judge from the standards of Pyle and Hoerr[1] the proximal epiphysis of the tibia is at least of "skeletal age" 13 years; the distal epiphysis of the femur is more difficult to assess from the published *x*-ray, but it is not inconsistent with skeletal age 13 years. Three maturity indicators are clearly visible in the head of the femur and pelvis, details of which have been observed in a study[2] of over 2,500 *x*-rays of healthy boys as summarized in the Table.

Age, to the Nearest Whole Year, at which Certain Percentiles of Over 2,500 Healthy Boys Showed Three Maturity Indicators in the Region of Hip-joint and Pelvis

Maturity Indicators	Age to Nearest Year		
	10%	50%	90%
Head of femur—stage 6	10	12	14
Greater trochanter—stage 5	11	13	14
Junction of ischial and pubic rami—stage 4 (i.e., completion of series)	6	9	13

Thus, in this region also, if we are to assume that the bones are male, their skeletal maturity is at least equivalent to those of an average boy of 13 years. A problem of a similar nature to this, but of historical rather than legal interest, was presented by the discovery in 1674 of immature bones in the Tower of London which are presumed to be the remains of Edward V and his brother. These bones have been re-examined during the present century.[3]—I am, etc.,

Dublin. ROY M. ACHESON.

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Syringe Services

SIR,—I note that in your annotation "Syringe Services" (*Journal*, January 11, p. 93) you discuss the satisfactory methods for the sterilization of syringes, in terms of hospital services, but make no comment as to the application of such services outside hospitals. My own efforts through the College of General Practitioners to interest the regional hospital boards in providing such a service for the use of general practitioners have met with no response whatsoever; and this omission from your annotation seems to me to stress the need for the medical establishment to organize their responsibilities in making available to individual practitioners those facilities of modern medicine which cannot possibly be provided by individuals.—I am, etc.,

London, W.1 B. S. COOPER.

Gastrectomy Specimens Wanted

SIR,—I should be grateful if you would allow me to use your correspondence columns for an appeal for pathological material. In the Nuffield Department of Clinical Medicine in Oxford we are interested in the site of formation of Castle's intrinsic factor and we need fresh frozen samples of the stomach of patients with pernicious anaemia for prosecuting these studies. These samples could be obtained during operations for gastric neoplasms. If any of your readers could kindly inform me when an operation for carcinoma of the stomach in a patient with pernicious anaemia was about to be done, giving preferably a few days' notice, I could make arrangements for the collection of the specimen at the operation.—I am, etc.,

Oxford. K. B. TAYLOR.

Obituary

R. K. BOWES, M.D., M.S., F.R.C.S., F.R.C.O.G.

Mr. R. K. Bowes, obstetric and gynaecological surgeon at St. Thomas's Hospital, died in that hospital on February 1, aged 53.

Robert Kenneth Bowes, the son of Dr. J. E. Bowes, of Grange-in-Borrowdale, Cumberland, was born on October 30, 1904. From Queen Elizabeth's Grammar School, Blackburn, he went on to the University of Liverpool to study medicine, and in 1929 he graduated M.B., Ch.B., with first-class honours, at Liverpool, and M.B., B.S., also with honours, at London. A brilliant student, he was awarded the Holt fellowship in physiology at Liverpool in 1928, and was gold medallist in obstetrics and gynaecology in his final year. After graduation he held resident appointments at the Liverpool Royal Infirmary. He took the F.R.C.S. in 1931, and proceeded M.S. (London) in 1932 and M.D. in 1935. With this fine record at his own teaching school, Mr. Bowes came down to St. Thomas's Hospital as surgical registrar in 1931. But his aim was to specialize in obstetrics and gynaecology, and he held both the junior and senior resident appointments in that department at St. Thomas's before he became first registrar and then chief assistant. He was also a demonstrator of anatomy and Louis Jenner research scholar. Eventually he joined the consultant staff as obstetric and gynaecological surgeon to out-patients. He was also on the staff of the Grosvenor Hospital for Women and was a consultant gynaecological surgeon to the South-west Metropolitan Regional Hospital Board. During the second world war he was a surgeon in the Emergency Medical Service.

In 1949 Mr. Bowes was Arris and Gale lecturer at the Royal College of Surgeons, choosing as his subject the superficial veins in the female and illustrating his remarks with infra-red photographic studies. He was the author of numerous papers, the editor of *Modern Trends in Obstetrics and Gynaecology*, and a contributor to the *Index of Treatment*, the *British Encyclopaedia of Medical Practice*, and the *Treatment of Medical Emergencies*. He examined for the Universities of Glasgow and London and for the Conjoint Board. In 1955 he was elected F.R.C.O.G.

Kenneth Bowes's untimely death will be a great sorrow to his friends and colleagues, and a serious loss to his specialty. A quiet, gentle, and unassuming man, he was a popular member of the staff at St. Thomas's. In recent years his health had not been good, and the very busy professional life he led did nothing to improve it. In 1935 he married Phyllis, daughter of the late Ernest W. Miller, of Fort Qu'Appelle, Saskatchewan, and she survives him with one son.

B. R. writes: Kenneth Bowes will be very sorely missed by his colleagues and many friends. My earliest memories of him are from his first days on the staff of St. Thomas's, when his teaching impressed me by its exhaustiveness: every possible facet of a problem was explored and discussed with the greatest clarity, so much so that, at times, there were many who were left far behind. His store of anecdotes to illustrate clinical problems was limitless and always apt and amusing. In fact, among his many great qualities his ability as a teacher was outstanding, both in his own specialty and also, during his earlier years, in general surgery.

In himself he was always a somewhat quiet and retiring personality, perhaps almost too much so, in that he was only infrequently seen at the various scientific meetings. When, however, he was present, either in this country or abroad, the phenomenal knowledge which he had of his subject was recognized and appreciated by all to be outstanding and, probably, unique. The onset of the war so soon after his appointment profoundly affected his life. It led to him settling in Surrey for the seven years of the evacuation from London. Here he became known and loved by a very large number of patients. At the end of the war he continued

to keep a home in the country—to which he retired every week-end—where he found happiness and relaxation with his family, music, and garden.

He was absolutely tireless in the care of his patients, and so conscientious that one could not help but feel that he was taking more out of himself than he could afford, particularly in the last few years when ill-health made his life difficult. The degree of his kindness, gentleness, and sympathy was such as to endear him to all who worked with him, and to all for whom he worked. It was a shining example which few will be able to equal. Others will write of his professional career, surgical skill, distinctions, and many learned publications: but all of us will remember him for his kindness, fairness, understanding, and the willingness and wisdom of his advice and help at all times.

C. J. S. O'MALLEY, C.B.E., M.B., B.S.

Group Captain C. J. S. O'Malley, formerly medical director of Garston Manor Rehabilitation Centre, died suddenly on January 25. During the war he was principal medical officer of the Desert Air Force before he was put in charge of the rehabilitation centres of the R.A.F.

Charles James Sidney O'Malley was born in Melbourne, Australia, in 1901. Educated at Wellington College and St. Thomas's Hospital Medical School, he qualified in 1925, taking the London degrees of M.B., B.S. ten years later. He was a formidable scrum-half at St. Thomas's, and had a trial for Ireland. If he had not joined the R.A.F. in 1926 and been sent forthwith overseas he might have had an Irish cap. After service in many parts of the world, in 1939 he was appointed senior medical officer at the headquarters of No. 11 Group, R.A.F. In 1940, at the Officers' Hospital, Torquay, he initiated what was to become the R.A.F.'s rehabilitation service. A year later he was appointed principal medical officer of the Desert Air Force, and in this command he organized the air evacuation of casualties—a remarkable achievement, for by 1944 over 21,000 casualties had been brought out of North Africa by returning aircraft. In 1944 he returned to Britain to co-ordinate the rehabilitation services of the R.A.F. At first he was commanding officer of the centre at Loughborough, but by the end of the war he was in charge of a further six centres. He was appointed C.B.E. in 1944.

A. P. H. R. writes: After his work at Torquay in 1940 Group Captain O'Malley's chief medical interest lay in the problems people experienced in recovering function and resettling themselves in work and in the home. He returned to administrative duties in the R.A.F. in 1947, but his heart was now entirely with rehabilitation, and so he retired from the service in 1950, when he was appointed by the North-west Metropolitan Regional Hospital Board to be the first director of Garston Manor Medical Rehabilitation Centre, the first general residential centre in the Health Service. Other appointments followed swiftly. He became adviser to the North-west Regional Hospital Board in physical medicine and rehabilitation and adviser to the south-east and eastern regions of the Ministry of Labour. From its opening in 1954 he directed the Medical Rehabilitation Centre, Camden Road, the first out-patient day centre in London. Appointed consultant in physical medicine to Queen Mary's Hospital, Roehampton, in September, 1955, he had to resign from Garston Manor with great regret because of the extent of his commitments. He was consultant adviser to the World Veterans Federation and often went abroad to advise the World Health Organization. He was to have gone to India soon at the request of the Indian Government.

With so much to do, nevertheless he always remained approachable and a sympathetic listener. Patients were made to feel that they were of individual importance and that life was worth living and full of purpose, no matter what disabilities had to be overcome or accepted. He became gravely ill quite suddenly on the morning of January 25 and died later that day. He is buried in the churchyard at Bishopstone within sight of his home. It is very hard to realize that no longer shall we hear that infectious gust of laughter or feel the warmth of that lovable personality. To his wife and two daughters and to his sister we offer our sympathy in their sudden tragic loss. His achievements remain as a memorial to a man who has served his country, his profession, and his patients so well.

FRANCIS EWART, O.B.E., M.B., B.Ch.

Dr. Francis Ewart, who was in general practice at Isleworth, Middlesex, for nearly thirty years, died suddenly on December 23, 1957, after an illness of two weeks. He was 65 years of age.

Francis Ewart was born in County Down, Northern Ireland, on March 12, 1894, the eldest of a family of six. He was educated at Campbell College and at the Queen's University of Belfast, where he graduated M.B., B.Ch. in 1916, with honours in medicine. During the first world war he served with distinction as a surgeon in the Royal Navy, being mentioned in dispatches and appointed O.B.E. From 1921 to 1930 he was in general practice at Burslem, Staffordshire, and then moved to Isleworth.

M. E. writes: Francis Ewart brought to general practice all the virtues of his profession and his personality. His clinical acumen, which was of a high order, combined with his unsparing and untiring care of his patients made him a practitioner of merit. As well as bringing his skill and experience to his work, his endless vitality and ready wit often proved a better tonic than any medicine he could prescribe. He did not suffer fools gladly, but to any who genuinely petitioned his help, not only within the confines of medical practice, his patience, kindness, and above all his generosity were boundless. To his colleagues he was a loyal and devoted comrade, willing as to all others to give his aid unstintingly. Although he was primarily a home and family lover, his interests extended in many other directions outside medicine. To horticulture, music, amateur dramatics, and to his great love, Rugby, at which game he excelled in earlier days, he gave his energy and enthusiasm. Frank Ewart epitomized in his nature and his work the best in his profession. Of him his patients could truly say he was their friend as well as their doctor, and it is as the former especially that many will miss him. To his widow and family we extend our deepest sympathy.

WACLAW KRASZEWSKI, M.D.

Dr. Waclaw Kraszewski died in Glasgow on January 11 after an illness of only a few hours. He was 53 years of age.

Waclaw Kraszewski was born at Wlocklawek, in the province of Warsaw, on October 7, 1904, and graduated M.D. at Cracow in 1929. He became an assistant in the department of surgery at the university, and held this position until 1939, when he joined the Polish Forces. After the defeat in Poland he escaped through Rumania to France, where he rejoined the Polish Forces. When France was defeated, his division was captured, but he escaped to the south of France and, later, was able to join the Allied Forces in Italy.

T. L. C. writes: Waclaw Kraszewski came to this country from Italy and became surgeon in charge of the Polish unit at Ballochmyle Hospital, Ayrshire. After the war the need for this unit decreased and Kraszewski's services were employed elsewhere. In recent years his work was chiefly in the urological units of Hairmyres Hospital and Ballochmyle Hospital. He was a most willing man, ready to oblige his colleagues in other units, and he never lost his skill in general surgery. His rapid, accurate operative technique was much admired and his judgment was respected. He had high standards of conduct which he did not hesitate to follow even when his action was to his own disadvantage. This was a feature of his early life in Poland and remained a feature in later years. He had great personal charm which was felt by his patients and by all sections of the hospital staff. His knowledge and use of standard English were excellent and he had also acquired some knowledge of the dialect of south-west Scotland. It was a source of great

pleasure to his colleagues, his patients, and to himself when he employed some unexpected expression in its exact context. A gifted colleague and a delightful friend has been lost, and for his widow and son there is heartfelt sympathy.

JANET R. MACPHAIL, L.R.C.P.&S.Ed.

Dr. Janet Macphail, for many years a medical missionary in India, and one of the founders of the Mure Memorial Hospital for Women at Nagpur, in the Central Provinces, died recently at St. Andrews, Fifeshire.

Janet Russell Macphail (formerly Wells) was the daughter of the Rev. James Wells, who became Moderator of the General Assembly of the United Free Church of Scotland, and was educated privately. She studied medicine at Edinburgh and at Queen Margaret College, a college for women students at Glasgow which became part of Glasgow University in 1892. After taking the Scottish triple qualification in 1893 she went to India as a medical missionary. Four years later she married the Rev. Dr. J. M. Macphail, also a medical missionary in India, who was well known for ophthalmic work. In the thirty years he was in the country he performed thousands of cataract operations, and in this and all his other work he had immense help from his wife. From 1924 onwards they were joined by one of their sons, Dr. Ronald Macphail. Dr. Janet Macphail continued her medical missionary work among women for some years after her husband's death, and then retired to St. Andrews. In addition to Dr. Ronald Macphail, there were four other children of the marriage, one of whom, Dr. Dugald Macphail, is in consultant practice as a psychiatrist in London.

G. G. MACDONALD, M.D.

By the death of Dr. G. G. Macdonald on January 21 the medical profession in the Middlesex boroughs of Wood Green and Southgate has lost one of its oldest and most highly esteemed members.

A son of the manse, George Grant Macdonald was born on June 13, 1879, the third son of the Rev. George Grant Macdonald, minister of the Free Church of Scotland at Cornhill, Banffshire. He was educated at Aberdeen Grammar School and at Aberdeen University, where he graduated M.B., Ch.B., with honours, in 1903, proceeding to the M.D., also with honours, two years later. After graduation he was awarded the Thompson travelling fellowship, and spent two years on postgraduate work, mostly in Germany at the University of Leipzig, and later with Professor William Bulloch in the pathology department of the London Hospital. He started practice in Wood Green and Southgate in 1905 and was still in practice at the time of his death fifty-two years later. Macdonald was a man of many interests, both professional and otherwise. In his early years in practice he was also bacteriologist to the Prince of Wales General Hospital at Tottenham for several years. Later for many years, until after the second world war, he ran his own private nursing-home where he did all his own surgery.

Throughout his professional life Macdonald was a keen member of the British Medical Association. On two occasions he was chairman of the North Middlesex Division, and for many years he represented the Division at the Annual Representative Meeting. Almost since its inception forty years ago he was a keen member of the Ganglion Club, a very active medical society in Wood Green and Southgate, and served one term as its president. A devoted member of the Worshipful Company of Barbers, he passed through all its offices, becoming Master in 1948. He represented the Barbers Company on the Epsom College committee for many years.

Rather retiring in disposition, Macdonald was a man of great energy, whole-heartedly devoted to his profession and of great kindness, so that to many of his patients he was not only a skilled physician but also a wise counsellor and friend. In private life his chief interests were his books, his pictures, and his garden. He was a great reader and possessed a great fund of general knowledge. He had amassed a large collection of pictures, mostly nineteenth century, of which he was very proud, but for many years his chief pleasure was in his beautiful garden, in which he spent most of his leisure hours. In 1907 Macdonald married Margaret Macdonald, of Knockbreck House, Tain, Rossshire. His wife died in 1953, and he is survived by two married daughters and one son, who has been in practice with him for twenty-one years.—M. M.

Medical Notes in Parliament

Hospital Waiting-lists

The MINISTER OF HEALTH, Mr. D. Walker-Smith, told Mrs. E. HILL (Manchester, Wythenshawe, C.) on January 28 that at the end of 1956 the number of patients awaiting admission to hospital was 431,000. This was the lowest recorded since the beginning of the Health Service. In the successive years the numbers had been (on December 31 in each year): 1949—498,000; 1950—531,000; 1951—504,000; 1952—500,000; 1953—526,000; 1954—474,000; and 1955—455,000. Sir FRANK MEDLICOTT (Central Norfolk, Nat. L. and C.) was informed that at the end of September, 1957, there were 434,000 people awaiting admission. The figures for the regions were:

Hospital Region	Number of Persons
Newcastle	28,282
Leeds	20,061
Sheffield	51,960
E. Anglian	12,977
N.W. Metropolitan	36,447
N.E.	26,583
S.E.	30,089
S.W.	39,771
Oxford	17,041
South Western	28,735
Welsh	30,547
Birmingham	41,063
Manchester	56,734
Liverpool	14,147

Mrs. Hill was also told that for patients (including tonsils and adenoids cases) treated in the ear, nose, and throat departments of non-teaching hospitals the average waiting time in 1955 was 167 days and in 1956 135 days.

Senior Medical Staff: Cost Per Bed

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Health for the annual average cost per in-patient bed of the services provided by consultants in each of the 14 regional hospital board areas during the financial year 1956–7 as regards hospitals for mental affection, for mental deficiency, and in hospitals for physical diseases, general and special, respectively. Mr. WALKER-SMITH, replying on January 29, said that information was not readily available in the form requested. He provided instead the following table relating to staffed beds of all types in non-teaching hospitals during the financial year 1956–7:

Region	Average Cost of Consultants' Salaries per Bed (All Types)	Average Cost of All Senior Medical and Dental Staff Salaries per Bed (All Types)	Approximate Amount Included for Salaries of all Senior Medical and Dental Staff in the Average Cost of Maintaining a Patient			
			Acute Hospitals	Chronic Hospitals	Mental Hospitals	Mental Deficiency Hospitals
	£	£	£	£	£	£
Newcastle	41·5	53·9	144·8	9·3	12·3	8·0
Leeds	28·4	38·2	151·3	4·5	9·1	4·3
Sheffield	33·6	46·0	155·9	3·5	13·4	6·5
East Anglian	36·5	48·2	175·4	7·6	12·6	7·8
N.W. Metropolitan	45·8	65·9	139·4	6·3	10·8	6·3
N.E.	40·4	56·4	154·9	9·7	11·9	8·4
S.E.	43·6	56·6	156·2	3·5	11·3	6·3
S.W.	30·3	43·1	142·5	5·8	11·5	8·2
Oxford	36·9	52·7	191·7	6·9	14·3	8·4
South Western	30·3	40·2	169·2	2·2	9·1	4·1
Wales	33·2	46·4	140·5	3·0	11·7	5·8
Birmingham	34·9	45·0	146·3	6·5	10·2	7·1
Manchester	28·5	40·0	147·6	3·9	6·3	3·0
Liverpool	33·6	48·5	121·2	3·5	10·2	14·5

Radioactive Fall-out

Mr. R. A. BUTLER, Lord Privy Seal, replying for the Prime Minister to Mr. FENNER BROCKWAY (Eton and Slough), who had referred him to an annotation on radiation in the *Lancet* of December 28, said he had examined the article carefully. It included information which was printed in a footnote to the report of the U.S. Congress joint committee on atomic energy published last August. This was a forecast. The possibility was mentioned of 10 to 25 strontium units if there was a predicted bending of the fall-out in the latitude of the north-eastern United States, and the footnote used the expression "if that occurs." It was a forecast, but it could not be proved to be correct. The British Government was working on the advice of the Medical Research Council's report. The present advice was that the highest strontium levels detected in bone in the United Kingdom were between 2.3 and 2.4 units. The present average figure was less than one unit. As the report said the danger limit should not be greater than 100 units, and that they should not begin to get anxious before the level of 10 units, he thought they were working within the level of what was sensible, on the basis of the best advice they could get.

Mr. K. ZILLIACUS (Manchester, Gorton, Lab.) said the figures quoted were regarded as controversial and subject to doubt by a great many scientists. Many said the safety limit was 10 units. The point was not the level of fall-out to-day, but how much strontium in the air would come down, without any further nuclear tests. Did not Mr. Butler leave to chance whether the scientists were correct who said the prevailing winds would bring it down here? Was he not giving the benefit of the doubt to the tests, over the lives of children? Mr. BUTLER replied that there was a possibility of every sort of doubt about scientific advice. The Government was perfectly modest in this. They were being guided by the best advice they could get from the M.R.C. reports, and at any time they could get further advice they would obtain it.

H-bombs in Aircraft

Mr. ZILLIACUS asked the Prime Minister whether, since it was now known that the crash of a hydrogen or atomic bomb-carrying aeroplane, followed by fire, could result in infecting an area of 100 sq. miles (259 sq. km.) or more with deadly, long-lived radioactivity from plutonium, he would forbid the carrying of nuclear weapons by aeroplanes in training or on patrol. Mr. GEOFFREY DE FREITAS (Lincoln, Lab.) asked what special instructions in the rendering safe of fused airborne nuclear weapons had been given to the appropriate Service and civilian first-aid and Civil Defence units in areas of the country which are regularly flown over by Royal Air Force and United States aircraft carrying nuclear weapons.

Mr. BUTLER said the question of Mr. Zilliacus was based on assumptions which did not accord with the scientific advice given to the Government on this subject. Nuclear weapons were at all times in a safe condition while they were being carried over this country. There was therefore no risk of a nuclear explosion and the question of special instructions about fused weapons did not arise. In the event of a crash of an aircraft carrying one of these weapons, the danger from radiation, in view of the strict precautions taken, was regarded as slight. It had not therefore hitherto been considered necessary to include in the standard instructions to Service and civil authorities on action to be taken in relation to crashed aircraft any special instructions relating to aircraft carrying nuclear weapons. These standard instructions were kept continually under review, and should it be necessary they would be added to and amended.

He also said in answer to further questions that there were occasions when such bombs were carried in an "unarmed" condition in transit, but these fortunately were not very frequent—he later used the word "rare." For strategic reasons he could not say anything further about other occasions on which they might have to be carried. Mr. H. GAITSKELL (Leeds, South, Lab.) complained about the confusion and anxiety caused by contradictory answers from Ministers, and asked for a clear statement on the circumstances and conditions in which H-bombs were carried and the control exercised by the Government over them. Mr. BUTLER promised to consider that.

Next M.R.C. Report

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked on January 30 when the Medical Research Council could be expected to issue its next report on the present dangers to health from radioactive fall-out, in view of the new and significant material now available. Mr. BUTLER stated that since the Medical Research Council issued its report in June, 1956, the United Nations Scientific Committee on the Effects of Atomic Radiation had made considerable progress in preparing its report to the General Assembly of the United Nations. This committee, composed of distinguished scientists from many countries, including the United Kingdom, had been collecting and collating information on all aspects of radiation affecting man and his environment, and was obliged to report not later than July 1 this year. The Medical Research Council would wish to consider this important document before reporting further itself. He added that he could not indicate when the United Nations committee was likely to report, but so far as the Government was concerned "the sooner the better."

Doctors' Cars Towed Away

Sir WAVELL WAKEFIELD (St. Marylebone, C.) asked the Home Secretary if he was aware that on December 27, 1957, on returning to his residence, Dr. J. G. Fairer left his car outside his residence in Wimpole Street, and, in spite of the car bearing a label "Charing Cross Hospital Staff," a British Medical Association badge, and a notice under the windscreen wiper saying where Dr. Fairer was, the police towed his car away without reference to the receptionist at Dr. Fairer's house, thus causing him to be nearly an hour late for his next appointment at Charing Cross Hospital; and if he would issue instructions to the police not to remove cars in this area bearing such labels without first communicating with the owner.

Mr. BUTLER said the Commissioner of Police had informed him that on December 17, 1957, Dr. Fairer's car was parked opposite a bombed site next to No. 42, Wimpole Street, in such a way as to cause serious obstruction. There were continuous lines of parked cars down both sides of the street and Dr. Fairer's car was one of three forming a third line. As the roadway was 27 ft. 3 in. (24.7 m.) wide, traffic had been reduced to a single line and heavy goods vehicles could not pass at all. The label and badge displayed on Dr. Fairer's car indicated that it was a doctor's car, but a small piece of paper bearing Dr. Fairer's name and address which was wrapped around the arm of the windscreen wiper was not noticed. The police, in accordance with their usual practice, had tried to find the owner before deciding to remove the car.

Sir WAVELL WAKEFIELD also asked why the police prevented Dr. Jerome Sturridge from collecting his car for one and a half hours at Paddington Green Police Station on January 1 after they had towed it away. Mr. BUTLER said that, according to the Commissioner of Police, Dr. Sturridge arrived at the police station to collect his car at about 12.50 p.m. and left with it at about 1.15 p.m. He was therefore at the station for about 25 minutes only. This time, which was spent in checking the car and its contents and in taking action in relation to the alleged offence of obstruction of the highway, could have been reduced if the owner had willed.

Alcohol and Road Accidents

In the House of Lords, Lord MATHERS asked the Government on January 29 whether a statement could be made about drink in road accidents, as the outcome of the report by the Medical Research Council and the Road Research Board. He was told by the Marquess of LANSDOWNE, Lord in Waiting, that the report would be available in a few weeks. There had been difficulties, in that some of the

analyses of part of the data had given equivocal results, which had meant still further research.

Notification of Lung Cancer

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Health whether, in view of the fact that alcoholic sclerosis of the liver was a notifiable disease and that in cases of death from it an inquest was sometimes held, he would consider making cancer of the lung also notifiable so that an inquest might be held where there was strong presumptive evidence of the association between this disease and cigarette smoking. Mr. D. WALKER-SMITH stated on January 29 that he assumed Mr. Hastings had in mind those deaths which were required to be reported to a coroner. Since neither an inquest nor a post-mortem examination could prove that in a person dying of cancer of the lung this had been caused by cigarette smoking, the reporting of such deaths to a coroner would seem to have no medical justification and would cause unnecessary distress.

Salk Vaccine from Canada

Mr. S. P. VIANT (Willesden, West, Lab.) asked how the four tons (4,064 kg.) of Salk vaccine which had arrived from Canada would be tested for purity before it was issued to the public. Mr. WALKER-SMITH replied on January 28 that the weight mentioned referred to a batch of vaccine as packed. In addition to the tests made by the manufacturers, samples of the vaccine had successfully undergone the necessary tests by the Medical Research Council before the batch was delivered in this country.

Recommended Alternatives

Mr. HASTINGS asked on January 27 what steps were taken by the Ministry of Health to make certain that preparations which doctors were recommended to prescribe instead of proprietary articles did contain drugs of good quality in the right proportion. Mr. R. THOMPSON, Parliamentary Secretary, replied that the *British Pharmacopoeia*, the *British Pharmaceutical Codex*, and the *British National Formulary* laid down standards with which all the standard drugs and preparations referred to were expected to comply.

Proportion of Administrators to Doctors

Dr. DONALD JOHNSON (Carlisle, C.) asked if the Minister was aware that, according to figures recently supplied, there was approximately one clerical and administrative officer to every doctor employed in the Health Service; and whether he would keep this fact under consideration in examining the future trends of the Service, particularly in view of the fact that there were a considerable number of doctors unable to find employment in it. Mr. THOMPSON told him that the Minister was aware that the numbers were in the approximate proportion stated, and he would continue to give to this fact such consideration as might be appropriate.

Smoking and Lung Cancer

Mr. M. LIPTON (Brixton, Lab.) asked the Chancellor of the Duchy of Lancaster on February 3 whether, in view of the failure of the Government's activities in letting the public know the facts about the connexion between smoking and lung cancer, he would reconsider the matter, especially in the light of the further evidence provided by the B.M.A. Dr. CHARLES HILL replied that by statements in Parliament, and the activities of local authorities, and directly through the Council for Health Education, the facts were clearly and widely known. It remained for individuals to reach their own decisions. Mr. TED LEATHER (North Somerset, Con.) said the facts were very much in dispute. There were strong grounds for thinking that the M.R.C. had stuck out their necks much too far. Dr. HILL: Although it is not a matter for me in my capacity as Chancellor of the Duchy, I may say quite plainly that the facts are fully known. The case has been fully established.

Mr. LIPTON asked the Minister of Health what further action he would take to publicize the connexion between cigarette-smoking and lung cancer. Mr. R. THOMPSON, Parliamentary Secretary, said that local health authorities were continuing to publicize the risks of smoking in their health education campaigns. It was still too soon to estimate the effect and to judge what further action was needed.

Poliomyelitis

Sir FRANK MEDLICOTT (Norfolk Central, Nat. Lib. and Con.) asked the Minister of Health if he was aware of the continued anxiety felt in seaside resorts as to the effect on health of the discharge of sewage into the sea, with particular reference to the risks of poliomyelitis; and if he would expedite the completion of the investigations by the Public Health Laboratory Service. Mr. D. WALKER-SMITH said he hoped that, in view of the absence of any real evidence of risk, there would not be anxiety in these areas. While there would be no avoidable delay, the Public Health Laboratory Service informed him that, by the nature of the investigations, it was impracticable to expedite them.

Mr. S. P. VIANT (Willesden, West, Lab.) asked what records would be kept of any damage to health done by the Salk vaccine. Mr. THOMPSON said that damage to health following an injection with Salk or British vaccine was most unlikely. Medical officers of health keep records of these injections, as of other immunizing procedures.

Cardiac Surgery

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked the Minister of Health when full facilities would be available in this country to enable surgeons to undertake the closure of ventricular septal defects in young children; and what estimate he had made of the number of people requiring surgical closure of ventricular septal defects.

Mr. WALKER-SMITH stated that this was a very difficult operation which was not ready for use outside a few centres in this country, and the information was not available to permit of an estimate of the number who might benefit from it. It followed that it was not possible to say when facilities for it were likely to become generally available.

Medico-Legal

ANDOVER FLUORIDATION ACTION

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The introduction of sodium fluoride into the Andover water supply[1] has caused controversy on the Andover Borough Council for nearly eighteen months. Last July a council motion to stop the practice was defeated by one vote, and an anti-fluoride association has been formed.

This body has now instituted legal proceedings against the Council.[2] These take the form of a "relator" action—that is, an action in which the Attorney-General, on the "relation" of a member or members of the public, sues to restrain the commission of a public mischief or to assert a public right. The writ claims that the fluoridation of the water supply was *ultra vires*, contrary to law and of no effect, and that the council had no power to introduce it or cause its introduction. The writ claims a declaration that the council have no power to supply water into which fluoride has been introduced, and an injunction to restrain them from doing so and from introducing fluoride into the water.

The injunction if granted is an order of the court which operates *in personam*, and if it is disobeyed those responsible are guilty of contempt and liable to answer for it by being personally committed to prison. It is thus one of the few remedies effective to curb administrative abuse. That you answer for your actions with your own personal liberty, and not only with a financial penalty which will be borne by someone else, is a salutary corrective. It means that once a public right is successfully asserted, or the existence of a public mischief successfully established, those who have denied the right or caused the mischief will continue to do so at their peril.

[1] *British Medical Journal*, 1956, **1**, 1348.
[2] *The Times*, January 31, 1958.

POLIOMYELITIS FROM SALK VACCINE
DAMAGES AGAINST CUTTER LABORATORIES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

During the last week in April, 1955, twenty-nine cases of poliomyelitis occurred in the United States in persons inoculated with Salk vaccine. Of these, all but three had received vaccine prepared by the Cutter Laboratories of Berkeley, California.[1] Four months later the U.S. Public Health Service made public the results of its investigations of the "Cutter incident": it was then known that 73 children out of the 400,000-odd inoculated with Cutter vaccine had developed poliomyelitis. These were cases which had occurred within 31 days of inoculation.[2]

Last month judgment was entered for the plaintiffs in two actions brought against the Cutter Laboratories by the parents of children who were disabled by poliomyelitis contracted after injections of Cutter vaccine.[3 4] Their case was that the children's illness was caused by the vaccine, which contained, as they alleged, live virus; that the Cutter Laboratories had been negligent in marketing the vaccine containing live virus; or, alternatively, that on the sale of each ampoule there was an implied warranty that the vaccine was safe.

Dr. J. E. Salk, who was called as an expert witness in support of the plaintiffs' case, gave evidence that at the time of the disaster and using the test procedures then in common use he had been able to produce safe vaccine containing no live virus every time and that other manufacturers had been able to do the same. The inference to be drawn from his evidence was that the Cutter Laboratories had been negligent. Dr. Wendell Stanley, a virologist and Nobel prize-winner, called for the defence, gave evidence that in the light of subsequent knowledge the 1955 testing procedures had been grossly inadequate, that the method of vaccine-making had been basically unpredictable, and that therefore the vaccine could have gone out containing live virus without any negligence on the part of the manufacturers.

The jury found that there was live virus in the vaccine injected into the two children and that it caused the disease. By a majority of 10 to 2 they decided that the manufacturers had not been negligent having regard to the conditions prevailing at the time. But by a majority of 11 to 1 they found that the defendants had impliedly warranted that the vaccine was safe and that the warranty had been broken. The damages which were awarded were $131,500 to the family whose child had both legs paralysed, and $15,800 for the other whose paralysis was limited to one leg. The defendants intend to appeal. Forty-four other actions arising out of the use of the vaccine at that period are said to be pending.

A.I.D.

Lord Wheatley, in his reserved judgment on January 10 on the question of whether A.I.D. amounts to adultery, said that the wife's pleading was open to criticism. He therefore adjourned the case for a fortnight to allow her to provide further particulars of the circumstances of the artificial insemination (*Journal*, January 25, p. 229). At the resumed hearing in the Court of Session at Edinburgh on January 29,[5] the wife's counsel intimated that his client declined to provide this information. Lord Wheatley therefore found that the defect in her pleading, which was a fundamental one, had not been cured, and ordered the case to be sent to the Undefended Roll.

Lord Blackford has put down a motion on A.I.D. for debate in the House of Lords on February 26.[6] He asks the House to declare that

"Artificial insemination of a married woman by a donor other than her husband is tantamount to adultery, that it should be sufficient ground for divorce, and that all children so conceived are illegitimate."

[1] *Brit. med. J.*, 1955, **1**, 1144, 1166.
[2] Ibid., 1955, **2**, 626.
[3] *The Times*, January 20, 1958.
[4] *Time*, January 27, 1958.
[5] *The Times*, January 30, 1958.
[6] *Manchester Guardian*, January 30, 1958.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 18** (No. 3) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	0	2			4	0	3	0	
Dysentery	671	135	105			477	49	226	2	1
Encephalitis, acute	5	0				3	0		0	
Enteric fever:										
Typhoid	2	0	0			5	2	1	0	1
Paratyphoid	7	0	0			2	0	1 (B)	0	
Food-poisoning	159	16	8			148	25	9	2	
Infective enteritis or diarrhoea under 2 years					29				9	27
Measles *	2,435	18	91		2	8,175	680	852	369	215
Meningococcal infection	23	5	10		1	30	4	12	0	1
Ophthalmia neonatorum	20	4	9			25	3	5	0	
Pneumonia †	1,059	96	420		12	516	31	320	14	1
Poliomyelitis, acute:										
Paralytic	22	1	4		4	30	3	2	0	9
Non-paralytic	9	2				11	4			
Puerperal fever §	196	38	36			210	35	9	1	1
Scarlet fever	679	44	74		13	693	35	83	30	18
Tuberculosis:										
Respiratory	606	78	107			612	79	118	27	
Non-respiratory	59	7	9			73	10	15	9	
Whooping-cough	444	20	45		4	2,664	121	479	13	74

DEATHS in Great Towns	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0			0	0	0	0	0
Dysentery	0	0				0	0		0	
Encephalitis, acute		0					0			0
Enteric fever	0	0	0			0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	2			3	0	1	0	0
Influenza	109	20	3			19	0	1	2	0
Measles		0	0				0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia	577	79	55			294	44	21	18	11
Poliomyelitis, acute	0	0				1	0			0
Scarlet fever		0	0				0	0	0	0
Tuberculosis:										
Respiratory	102	11	10			55	5	11	2	0
Non-respiratory		0	0				1	0	0	1
Whooping-cough	1	0	0			0	0	0	0	0
Deaths 0–1 year	264	35	37			222	32	32	13	5
Deaths (excluding stillbirths)	7,987	1113	779			5,913	847	674	151	174
LIVE BIRTHS	8,329	1239	1028			7,746	1135	978	230	396
STILLBIRTHS	198	22	27			209	22	29		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Venereal Diseases

In England and Wales during the quarter ending September 30, 1957, 1,240 new cases of syphilis were reported as attending the clinics. Of these, 200 were classified as primary, secondary, or latent in the first year of infection, 9 cases of congenital syphilis in children aged under 1 year were reported, and 133 cases in persons over that age. New cases of gonorrhoea numbered 7,155, of chancroid 66, and of non-gonococcal urethritis (males only) 4,408.—*Monthly Bulletin of the Ministry of Health*, January, 1958.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in December was 117, compared with 116 in the previous month and 115 in December, 1956.

The numbers of cases of industrial diseases in the United Kingdom reported during December, 1957, were as follows: lead poisoning 3, aniline poisoning 2, anthrax 5, epitheliomatous ulceration 40, chrome ulceration 21; total 71. There were 9 deaths from epitheliomatous ulceration, 8 due to pitch and tar, and 1 due to mineral oil.—*Ministry of Labour Gazette*, January, 1958.

Week Ending January 25

The largest rises in the number of notifications of infectious diseases in England and Wales during the week ending January 25 were 158 for dysentery, from 671 to 829, 142 for scarlet fever, from 679 to 821, and 127 for whooping-cough, from 442 to 569; the largest falls were 142 for acute pneumonia, from 1,059 to 917, 97 for measles, from 2,435 to 2,338, and 32 for food-poisoning, from 159 to 127.

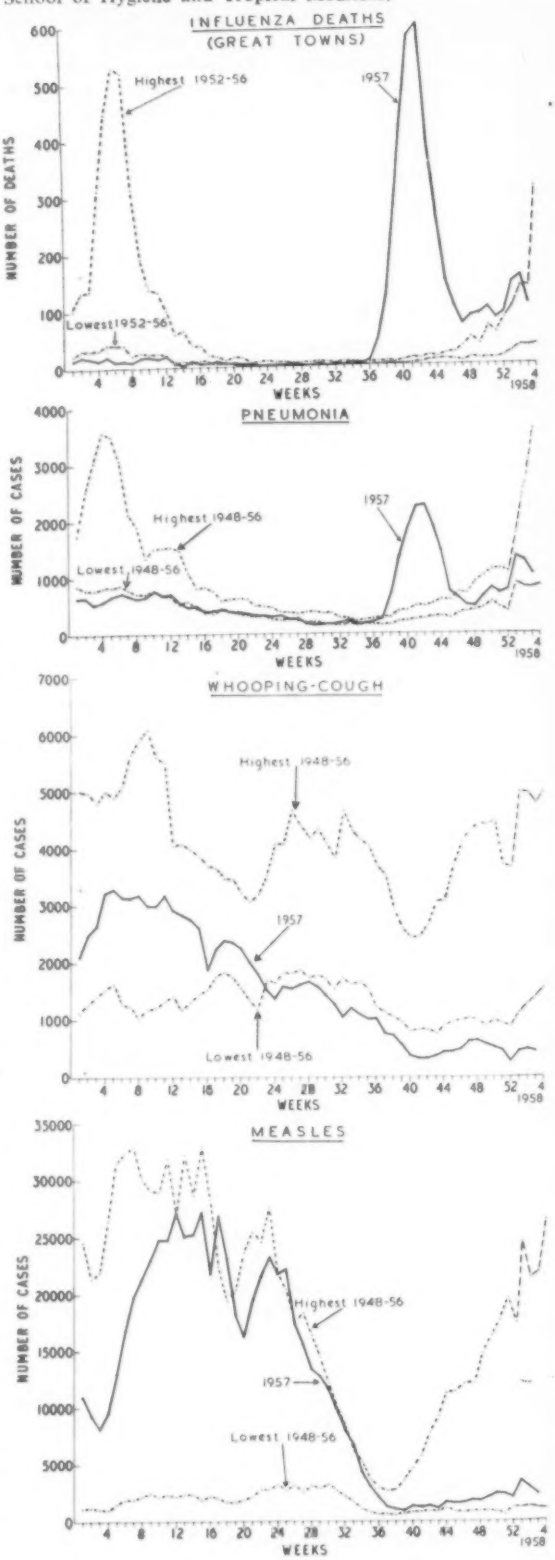
A small fall in the incidence of measles was recorded in most areas; the largest was in Wales, where a fall of 93, from 563 to 470, was recorded. The chief exception to the general fall in the incidence of measles was a rise of 79 in Lancashire, from 138 to 217; the largest rise within this county was 44 in Ulverston R.D., from 4 to 48. A small rise in the notifications of scarlet fever was recorded throughout the country. Only small changes were recorded in the local trends of whooping-cough. 1 case of diphtheria was notified compared with 2 in the preceding week.

24 cases of acute poliomyelitis were notified, and these were 4 fewer for paralytic and 3 fewer for non-paralytic cases than in the preceding week. The largest returns were 3 cases in London, Yorkshire West Riding, and Southampton County (Winchester M.B. 2).

For the fourth consecutive week the numbers of notifications of dysentery have increased. The chief features of the returns during the week were a rise of 250 in Lancashire and a fall of 73 in London. The largest centres of infection were Lancashire 456 (Oldham C.B. 141, Middleton M.B. 37, Preston R.D. 37, Royton U.D. 36, Liverpool C.B. 33, Manchester C.B. 33, Blackburn R.D. 26, Denton U.D. 16, Salford C.B. 13, Rochdale C.B. 11, St. Helens C.B. 10, Whiston R.D. 10), Yorkshire West Riding 99 (Thorne R.D. 22, Bradford C.B. 21, Sheffield C.B. 19, Huddersfield C.B. 11), London 62 (Islington 14, and the other 48 cases were scattered through 17 boroughs), and Cambridgeshire 19 (Cambridge M.B. 17).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the years 1948–56 (influenza, 1952–6) are shown thus - - - - - -, the figures for 1957–8 thus ————. Except for the curves showing notifications in 1957–8, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Medical News

Group Ophthalmic Unit.—On February 4 Sir STEWART DUKE-ELDER opened a Group Ophthalmic Centre at Neasden Hospital. This 26-bed Centre will provide in-patient facilities for three hospitals of the Central Middlesex Hospital Group—the Central Middlesex, Willesden General, and Acton Hospitals. The Centre will not be concerned with out-patients. Speaking at the opening, Sir Stewart Duke-Elder said that the event was not only a local but a national affair. It was a landmark in good medical planning. Ten years ago the Faculty of Ophthalmologists, when asked for a blue-print for an ideal eye-service for the nation, had recommended the Ministry of Health to set up regional ophthalmic surgical centres, each with a minimum of 25 beds, to replace the existing pattern of small pockets of ophthalmic beds scattered here and there in general wards. In ophthalmology particularly specialization was essential for the best treatment and for progress, and such centres would make this possible. In this way the patient would have the benefit of highly experienced surgery and nursing. "We suggested all this to the Ministry some 10 years ago, but they did nothing." Three years ago the first ophthalmic unit of this type was established at the South Middlesex Hospital, and it was doing magnificent work. Thanks to the initiative of the North-west Metropolitan Regional Board and the Central Middlesex Group Committee there was now this second unit. "It is because I hope that all England will do to-morrow what this regional board has done to-day, that I have come on this occasion," said Sir Stewart.

Lady Tata Memorial Trust.—The Trustees of the Lady Tata Memorial Fund invite applications for grants, scholarships, or fellowships for research on diseases of the blood, with special reference to leukaemia, in the academic year beginning on October 1, 1958. Candidates with programmes of research on any aspect of malignant disease which may throw incidental light on problems of leukaemia will also be eligible for consideration. The Trust's awards are open to suitably qualified investigators of any nationality, working in any country in which it will be possible to make payments in the coming academic year.

Grants of variable amount are made for research expenses or to provide scientific or technical assistants for senior workers. Scholarships are awarded for the personal remuneration of workers carrying out approved research under suitable direction; their normal value will be £600 sterling per annum for whole-time research, with proportional adjustment for work on a part-time basis. In addition the Trustees may award one or more Lady Tata memorial research fellowships to workers with considerable research experience; the stipends of these fellowships will be at the rate of £1,200 sterling per annum.

Further particulars and forms of application may be obtained from the secretary of the (European) Scientific Advisory Committee, Lady Tata Memorial Trust, Chester Beatty Research Institute, Fulham Road, London, S.W.3. Applications must be submitted before March 31. The awards will be announced by the Trustees in June.

Yugoslav Medical Delegation.—A delegation from the Yugoslav Ministry of Health has arrived in the United Kingdom to examine British methods for the control of poliomyelitis and the production of the vaccine. The visit was arranged by the British Council. The delegation will visit the Ministry of Health, laboratories of the Medical Research Council and of the firms making the vaccine, a clinic where immunization is carried out, and hospitals where cases of poliomyelitis are treated. The medical members of the delegation are Dr. D. ANTONIJOVIC, director of Serbia's Institute of Hygiene, Dr. B. BORDJOSKI, chief of the Institute's virology department, Dr. LJ. STOJKOVIC, physician at the Institute's virology department, and Dr. D. KALIC, epidemiologist of the Federal Institute of Public Health.

R.C.P. Edinburgh.—The Royal College of Physicians of Edinburgh held its biennial dinner on January 24. Among those present were the Lord Provost of Edinburgh, the Secretary of State for Scotland, and the presidents of other Royal Colleges and of the Royal Faculty of Physicians and Surgeons, Glasgow. The vice-president of the College, Dr. J. D. S. CAMERON, proposed the toast of the City of Edinburgh, and the Lord Provost, Mr. IAN A. JOHNSON-GILBERT, replied. The toast of the "Sister Professions" was proposed by Dr. J. K. SLATER and replied to by the Rev. Dr. JOHN A. FRASER and Lord GUEST. The Secretary of State for Scotland, Mr. J. S. MACLAY, proposed the toast of the Royal College of Physicians of Edinburgh, which was answered by the president, Dr. A. RAE GILCHRIST.

"Journal of the College of General Practitioners."—This month sees the appearance of the first issue of the *Journal of the College of General Practitioners*, with which is combined the College's *Research Newsletter* No. 18. This issue contains 104 text pages between plain grey covers and costs 3s. 6d. The journal is expected to appear quarterly. The honorary editor and assistant editor are, respectively, Dr. R. M. S. MCCONAGHEY and Dr. J. F. BURDON, and their address is Prospect House, Dartmouth, Devon. The editorial board consists of Dr. G. F. ABERCROMBIE, Dr. D. G. FRENCH, Dr. J. H. HUNT, Dr. R. J. F. H. PINSENT, and Dr. G. I. WATSON. The contents of the journal include editorials, lectures, original articles, research reports, College news, book reviews, and abstracts.

W.H.O. Budget.—The executive board of the World Health Organization has recommended a working budget of $14.2m. for 1959. This recommendation will be submitted to the eleventh World Health Assembly, which opens in Minneapolis on May 28. This is an increase of $700,000 over the effective working budget agreed upon by the tenth World Health Assembly for 1958.

M.R.C.P.—At the quarterly comitia of the Royal College of Physicians of London on January 30 the following, having satisfied the Censors' Board, were elected members of the College:

K. R. Aberdour, C. P. Anyon, R. R. Ashby, K. M. Barber, W. Beck, H. S. Bedson, F. W. Best, R. M. Buckle, P. J. A. Butcher, A. R. Chrispin, P. J. Dally, E. Davidson, P. C. Farrant, J. K. Finlayson, R. Finn, S. B. Furnass, P. C. Gautier-Smith, P. W. Gilman, R. J. Goetz, D. N. Gupta, M. J. Harris, W. D. Hayley, W. Hindle, I. B. Houston, G. Howitt, J. A. Ireland, R. A. Irvine, P. H. Kendall, A. V. Kurta, A. F. Lever, Kee Jin Lim, B. P. Maclaurin, J. M. Marks, D. Mattingly, T. O. Ogunlesi, L. H. Opie, E. H. O. Parry, R. Porter, I. Rachman, V. J. Richardson, M. Ll. Rutter, J. W. Scopes, T. Selby, A. K. N. Sinha, D. R. Smith, M. L. Thomas, C. F. H. Vickers, J. M. Ward, P. K. G. Warren, E. D. West, D. E. L. Wilcken, V. Wright, and N. R. W. Wynn-Williams.

Multiple Sclerosis Survey.—The National Institute of Nervous Diseases and Blindness, Bethesda, is sponsoring a survey of multiple sclerosis and certain other nervous diseases in two cities of comparable populations but different latitude in the North American continent and in Japan. Dr. R. S. ALLISON, neurologist to the Royal Victoria Hospital, Belfast, has recently completed a survey of Charleston County, South Carolina, and in the summer will visit Halifax, Nova Scotia, for the same purpose. Dr. DOUGLAS MCALPINE has joined a team from Tokyo University which will spend three months in Kumamoto and the same period in Sapporo.

Work in Compressed Air.—Last month Mr. IAIN MACLEOD, Minister of Labour and National Service, published regulations to protect the health and safety of men employed on work in compressed air. These regulations (S.I. No. 61, 1958, H.M.S.O., price 8d. net) will come into operation on April 21. They are designed to ensure that close attention is paid to the health and safety of those working in compressed air, and in particular that compression and decompression are properly controlled and supervised. Detailed rules for these procedures are contained in a schedule to the regulations. In this way it is hoped to reduce the incidence of caisson disease ("the bends").

COMING EVENTS

Mental Deficiency.—Dr. J. VAN DEN BOSCH, of the Netherlands Instituut voor Praeventieve Geneeskunde, Leyden, will lecture at University College, London, on February 7 at 5 p.m. (in the eugenics lecture theatre). His subject will be "A Mental Deficiency Syndrome in a Dutch Family."

Radio.—"Children in Hospital" in the B.B.C. series "Parents and Children," February 10, 7 p.m. in Network Three.

Medical Art Society.—Sixteenth annual exhibition at Walker's Galleries, 118, New Bond Street, London, W.1, February 13 to March 5, 10 a.m. to 5 p.m. weekdays, Saturdays 10 a.m. to 1 p.m.

Hunterian Society.—Annual dinner, February 13, at the Savoy Hotel, Strand, W.C.2. Tickets (35s.) from Mr. GEORGE QVIST, F.R.C.S., 72, Harley Street, W.1.

Reticuloendothelial Society.—Second symposium, August 29–31, at Rapallo, Italy. Proposed titles of papers from intending participants, with a short summary in English, should be sent before March 15 to Dr. ALBERTO MARMONT, Clinica Medica Universitaria, Viale Benedetto XV, Genova. Dr. Marmont will also receive applications for attendance as observers.

Faculty of Medicine, Barcelona.—Second course on asthma and allergy, March 20–27. Details from Dr. J. FARRERONS-CO, 343, Consejo de Ciento, Barcelona.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

All the journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Medical and Biological Illustration.—Issued quarterly (£3 annually). The new issue, Vol. 8, No. 1, includes:

THE TRAVELLING EXHIBIT. P. Hansell, H. Grayshon Lumby, and C. R. Brecknell.
THE KODAK SHORT RUN COLOUR SYSTEM OF LITHOGRAPHY. Robert Ollerenshaw.
PHOTOMICROGRAPHY BY ELECTRONIC FLASH. Ronald Plummer.
CLEAN ANATOMICAL SPECIMENS. David Brown.
AN ENDOGASTRIC CAMERA. Arthur Smialowski and Paul O'Sullivan.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 10

GUY'S HOSPITAL.—5 p.m., Endocrine Demonstration: Diabetes Insipidus. Guest speaker, Dr. O. Garrod.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor J. McMichael: Heart Failure.
UNIVERSITY COLLEGE LONDON.—At Chemistry Lecture Theatre, Gower Street, W.C., 5.30 p.m., special university lecture in physiology by Professor A. Szent-Györgyi (Massachusetts): Bioenergetics—(1) General Principles.

Tuesday, February 11

B.B.C. TELEVISION.—9.30 p.m., "Your Life in Their Hands," No. 1—The Breath of Life, from the Churchill Hospital, Oxford.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor J. M. Yoffey: Some Problems of Lymphoid Tissue.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Differential Diagnosis of Mycotic Diseases of the Skin.
MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Small Theatre, Clinical Sciences Building, York Place, Manchester, 8 p.m., Thoracic Evening. Mr. I. F. Dark: Air-traps following Operations on the Neck; Mr. K. Douglas: Some Aspects of Cardiospasm; Mr. J. S. Glennie: Value of a Chest X-ray.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Sir Francis Fraser: Practice of Medicine: Past, Present, and Future.
ST. ANDREWS UNIVERSITY.—At Physiology Lecture Theatre, 6 p.m., Professor A. S. Prophet: Infections of the Mouth.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. D. J. MacRae: Films demonstrating (1) Forceps Delivery; (2) Replacement Transfusion; (3) Normal Labour; (4) Caesarean Section.
UNIVERSITY COLLEGE LONDON.—At Chemistry Lecture Theatre, Gower Street, W.C., 5.30 p.m., special university lecture in physiology by Professor A. Szent-Györgyi (Massachusetts): Bioenergetics—(2) Applications.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Clinical Neurology (Part I).

Wednesday, February 12

BEDFORD COLLEGE.—5.15 p.m., public lecture by Dr. D. M. MacKay, Ph.D.: The Human Brain—The Brain as an Information System (Illustrated).
● INSTITUTE FOR THE STUDY AND TREATMENT OF DELINQUENCY.—At St. George's Institute, 7.30 p.m., Mr. Peter Kuenstler, M.A.: Employment Problems.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: Genetic Principles.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. W. P. Cleland: Benign Intra-thoracic Tumours.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. G. Hanley: Disorders of Micturition in Females.
LONDON UNIVERSITY.—At Guy's Hospital Medical School, 5 p.m., special university lecture in human anatomy and morphology by Professor C. H. Waddington, F.R.S.: Evolutionary Adaptation to Environmental Stress.
MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Manchester University, 4.30 p.m., Presidential Address by Mr. H. Varley: Corticosteroids—Their Determination and Clinical Significance.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Lecture by Dr. H. Lehmann.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Professor F. A. R. Stammers: Mechanical Factors in Post-gastrectomy Problems.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Walker Lecture by Professor Claude Rimington, D.Sc., F.R.S.: Some Aspects of Haemoglobin Biosynthesis and Their Importance to Medicine.

Thursday, February 13

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Dr. I. Frost: Sulphonamide Aids to Psychotherapy.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor A. Neuberger, F.R.S.: Enzymes in Health and Disease.
GLASGOW UNIVERSITY AND ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—At Royal Faculty of Physicians and Surgeons, 3 p.m., conference on obstetrics and gynaecology. Dr. J. Hewitt, Dr. H. Stirling, and Dr. W. C. Armstrong: Operative Treatment of Prolapse.
● HUNTERIAN SOCIETY.—At Savoy Hotel, Strand, W.C., 7 for 7.30 p.m., annual dinner.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: Genodermatoses.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., joint meeting with Liverpool Society of Anaesthetists. Dr. J. W. Dundee: Man-made Maladies.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Marc Daniels Lecture by Dr. A. L. Cochrane: Meaning of the *X*-ray Classification of Coal-workers' Pneumoconiosis.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION: (1) CHILD PSYCHIATRY SECTION.—At 11, Chandos Street, W., 6 p.m., Dr. H. Dugmore Hunter and Dr. R. F. Barbour: Advantages or Otherwise of the Physical Examination of a Child Patient by His Psychiatrist. (2) PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION.—At 11, Chandos Street, W., 8 p.m., Sister Mollie Clark: Role of the Charge Nurse in the Mental Hospital.
ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Physiology Department, Queen's College, Small's Wynd, Dundee, 5 p.m., Professor R. E. Tunbridge: So-called Collagen Diseases.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. F. H. C. Crick: Nucleic Acids—(1) Structure.

Friday, February 14

● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. W. N. Goldsmith: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Scadding: Clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. W. McKenzie: Stapes Mobilization.
MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, near Birmingham.—8 p.m., Professor Alfred Meyer: Fact and Myth in Prefrontal Leucotomy.
PLYMOUTH MEDICAL SOCIETY.—At Greenbank Road Hospital, 8.30 p.m., clinical evening. (Cases from 8 p.m.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. Norman Tanner: Diagnosis and Treatment of Oesophageal Bleeding. (2) 4 p.m., Dr. A. Rae Gilchrist: Heart Block.
ROYAL INSTITUTION.—9 p.m., Professor J. Z. Young, F.R.S.: Structure of Cells.
ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., dissertation by Mr. A. Milne: Poliomyelitis.
SOCIETY OF MEDICAL OFFICERS OF HEALTH (WELSH BRANCH).—At B.M.A. House, 195, Newport Road, Cardiff, 6.30 p.m., Dr. F. Marie Richards: Perinatal Mortality.

Saturday, February 15

BIOCHEMICAL SOCIETY.—At Beveridge Hall, Senate House, University of London, 10.30 a.m., symposium: Glutathione.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Eton.—On January 22, 1958, at the Maternity Hospital, Cambridge, to Ilse (formerly Ursell) and Bruce Eton, M.D., M.R.C.O.G., a son—David Alexander.
Jackson.—On January 15, 1958, to Eileen, M.B., B.S., wife of John W. Jackson, M.Ch., F.R.C.S., of "Cressingham," Marsham Way, Gerrards Cross, Bucks, a son—Adam John Greenwood.

DEATHS

Buchan.—On January 19, 1958, at 57, Clarkegrove Road, Sheffield, Yorks, William Taylor Buchan, M.B., Ch.B.
Chamberlain.—On January 20, 1958, at The Rectory, Dun Laoghaire, Eire, George Harry Amyrald Chamberlain, M.D., M.R.C.P.I., D.P.M., aged 38.
Fraser.—On January 13, 1958, Robert Gibson Fraser, M.B., Ch.B., of 223, Birchfield Road, Handsworth, Birmingham, Warwicks.
Grant.—On January 10, 1958, at 57, Druids Lane, Birmingham, Warwicks, May Isabella Turner Grant, M.B., Ch.B., D.P.H.
Hallowes.—On January 20, 1958, at Ashwood, Hartington Street, Leeks, Staffs, Arthur Collis Hallowes, *M.C.*, M.B., B.Ch., aged 72.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Magnesium Sulphate in Coronary Thrombosis

Q.—*Workers in South Africa have reported*[1,2] *dramatic clinical improvement in cases of coronary thrombosis following the administration of parenteral magnesium sulphate, and in the majority of cases reversion of abnormal lipoprotein patterns to normal. Has this work been confirmed, and, if so, what are the rationale and indications for this therapy?*

A.—There are two possible explanations for the reputedly beneficial effect of magnesium injections in ischaemic heart disease. One is an anticoagulant effect of magnesium ions, which have been shown by Greville and Lehmann[3] to inhibit clotting *in vitro* by competing with calcium ions. The second is the reduction of serum beta-lipoprotein, since this band corresponds to the Sf 12-20 fraction described by Gofman[4] as having an important bearing on the development of coronary disease. However, this view has been challenged by other workers,[5,6] and the changes shown by the South African writers are difficult to interpret in the absence of information about the alpha-lipoprotein.

The clinical effects of magnesium sulphate therapy are also difficult to assess. The progress in cases of recent infarction, as described by Malkiel-Shapiro *et al.*,[1] does not differ materially from that seen in many patients on bed rest only. The improvement in patients with angina is more convincing, but the effect of control injections (for example, saline) was not tried, and the number who stopped treatment because of failure to improve is not stated. No confirmatory study appears to have been published since, but this form of therapy has previously been reported in the Russian literature.[7] In the absence of confirmation of this work, it is not possible to define the indications for magnesium sulphate therapy.

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2. Bersohn, I., and Oelofse, P. J., *Lancet*, 1957, **1**, 1020.
3. Greville, G. D., and Lehmann, H., *J. Physiol.*, 1944, **103**, 175.
4. Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A., and Strisower, B., *Circulation*, 1950, **2**, 161.
5. Paterson, J. C., Cornish, B. R., and Armstrong, E. C., ibid., 1956, **13**, 224.
6. Cooperative Study on Lipoproteins and Atherosclerosis, Discussion B, ibid., 1956, **14**, 720.
7. Peplia, A. N., *Sovetsk. Med.*, 1956, **20**, 63.

Diagnosis of Haemolytic Disease of the Newborn

Q.—*How can jaundice due to ABO incompatibility be diagnosed in the newborn and differentiated from physiological jaundice?*

A.—In mature infants jaundice in the first 24 hours of life is almost always due to haemolytic disease of the newborn. In general, the sooner after birth that jaundice occurs and the greater its severity, the more likely is it to be due to haemolytic disease of the newborn and the less likely is it to be physiological.

When jaundice develops within the first 24 hours the direct Coombs test should be performed. If it is strongly positive the infant probably has haemolytic disease of the newborn due to anti-Rh; if the test is negative or only weakly positive, it may well have haemolytic disease of the newborn due to ABO incompatibility, but further tests must be made to establish the diagnosis. The first step is to establish that the infant is group A (or B) and that the mother is O (haemolytic disease of the newborn due to ABO incompatibility is hardly ever encountered except in the offspring of group O mothers). Next, the ability of the mother's serum to haemolyse a 5% suspension of the infant's cells, after one hour at 37° C., must be tested. A negative result virtually excludes the diagnosis. Finally, haematological signs must be sought in the infant: usually a drop of its whole blood, when spread on an opal tile, will agglutinate spontaneously within five minutes. A blood film almost always shows microspherocytosis and the osmotic fragility of the red cells is increased.

In severe and moderate cases the reticulocyte count is above normal limits during the first two or three days of life. The haemoglobin concentration is often at the lower end of the normal range and may even be as low as 12 or 13 g./100 ml. In mild cases the infant's haematological signs may be equivocal and it may be impossible to do more than suspect the diagnosis.

Storage of Vaccines and Sera

Q.—*For how long do immunizing agents retain their potency (1) in a domestic refrigerator, (2) without refrigeration in a temperate climate, (3) without refrigeration in the tropics (up to 115° F. (46.1° C.) in the shade)?*

A.—It is difficult to give exact information on the duration of potency of vaccines, toxoids, and sera. Many manufacturers provide an excess to cover some deterioration during storage under adverse conditions. The recommendations of the makers should always be followed. It is a good rule to keep the prophylactics and sera in an ordinary refrigerator running at about 4° C. (except fluid smallpox vaccine lymph and yellow-fever vaccine, which may safely be frozen). It is unwise to expose any agents to tropical temperatures except for short periods during transit.

Prophylactic	Time Potency Retained		
	In a Domestic Refrigerator (4–10° C.)	At Room Temperature in a Temperate Climate	In the Tropics at up to 115° F. (46·1° C.) in the Shade
Glycerinated vaccine lymph	2 weeks	Not more than 1 week	Possibly a few hours only
Dried vaccine lymph (Lister)	Indefinitely	At least 1 year	At least 1 month
T.A.B. (phenolized)	2 years	6 months	1 month
T.A.B. (alcoholized)	Indefinitely	It is generally recommended that the vaccine should be kept at about 4° C. at all times, but recent work suggests the vaccine may be more stable at room temperature than was at first supposed	
F.T. (formol toxoid)	1 year	Probably 6 months in a cool cellar	Not known, probably considerable variation with different batches
T.A.F. (toxoid-anti-toxin floccules)	2 years	2 years	3 months
A.P.T. and P.T.A.P.	2 ,,	18 months	Not accurately determined
Tetanus toxoid	2 ,,	2 years	Not accurately determined
Pertussis vaccine	2–3 ,,	6 months	Not accurately determined—but less than 3 months
Cholera vaccine	18 months	3 ,,	2 weeks
Yellow fever vaccine	1 year	1 month	Deteriorates rapidly
Poliomyelitis vaccine	At least 6 months	Recommended that at no time should the vaccine be exposed to a temperature of more than 68° F. (20° C.)	
B.C.G. (liquid)	2–4 weeks	Must be used as soon as possible after manufacture, and always kept away from direct sunlight	
B.C.G. (freeze-dried)	At least 3 months	Probably 3 months	Deteriorates rapidly
Refined therapeutic sera	5 years in sealed glass ampoules, 2 years in rubber-capped bottles	Perhaps 3 years in a cool room in glass sealed ampoules	Not accurately determined

The above table is meant to give general guidance. The periods mentioned give a considerable margin of safety.

Facial Hair

Q.—*A girl, aged 16, has hair protruding from her nostrils, and recently this has become more noticeable. She also has some facial hair. What treatment should be given?*

A.—Abnormalities of facial hair following puberty often correct themselves after adolescence. It is therefore inadvisable to embark on any radical treatment. Temporary

treatment by depilatory or cutting is harmless. Electrolysis would probably be desirable if the condition persists into adult life.

Greasy Hair in Pregnancy

Q.—*During her first pregnancy a patient noticed that her hair became unusually greasy. In her second her hair became so greasy that it needed washing every five or six days, and the condition has now persisted for two years after the birth. Previously her hair was normal. What is the explanation, and what treatment is advised?*

A.—In both sexes the amount of sebum excreted increases gradually towards puberty. After puberty there is a continuing slight rise until the age of about 25 years, and thereafter the levels remain fairly constant. In women, however, there is a significant drop in sebum excretion as they become more elderly. The amount of sebum and the activity of the sebaceous glands have been shown to be increased by luteinizing hormone, so an increase in the grease content of the hair during pregnancy might reasonably be due to the increased luteal activity during this period. It has also been shown in some cases that increased sebum excretion and acne are associated with luteinization of the ovaries, so in the case described one would suppose that the luteinization had not regressed to its original state.

I think it would be unwise to tamper with this patient's endocrine balance on account of such a relatively insignificant symptom. The only treatment I would advise would be that generally prescribed for excessive greasiness of the hair and seborrhoea—that is, the frequent use of one of the defatting shampoos such as spirit soap or one of the proprietary preparations.

Taking the Temperature

Q.—*What differences may be expected in temperatures taken in the mouth, under the axilla, and in the rectum? Which is the most reliable indicator of the true body temperature? May cases of low fever be missed with axillary readings?*

A.—Pembrey, in Schäfer's *Text Book of Physiology*, 1898 (Vol. 1, p. 788), gives the following average figures for the mean temperatures in a working day:

Rectum	37.2° C.
Axilla	36.9° C.
Mouth	36.87° C.

It would be difficult to define the term true body temperature. Eichna and others[1] give the following mean deviations from rectal temperature:

Pulmonary artery	−0.26° C.
Right ventricle	−0.23° C.
Inferior vena cava	−0.26° C.
Hepatic veins deep in the liver ..	−0.03° C.

There is now a good deal of evidence that the rectal temperature is higher than arterial blood temperature. It is not known why. If the temperature is carefully taken in the axilla there is no reason to expect that cases of low fever will be missed, though it is possible that excessively low readings may be obtained in the first stages of rigor.

REFERENCE

1 Eichna, L. W., *et al.*, *J. clin. Invest.*, 1951, **30**, 353.

NOTES AND COMMENTS

Ethyl Chloride, Nitrous Oxide, and Oxygen Mixture.—Mr. VICTOR GOLDMAN (London, W.1) writes: Your expert ("Any Questions?" January 25, p. 236) has suggested that a small hole is necessary for squirting ethyl chloride into a McKesson or similar apparatus when adding it to nitrous oxide-oxygen mixture. He has omitted to mention that this small hole would have to be fitted with a one-way valve—a spring-loaded ball-bearing has been used for this purpose—otherwise inefficient anaesthesia would result from air dilution. However, there is a much more simple method, for your questioner particularly mentions dental anaesthesia. In these cases a nose-piece is employed, and it is the usual practice of most dental anaesthetists to use the mouth pack as a mouth cover. This is convenient, for at the appropriate time a small quantity—about 2 ml.—of ethyl chloride can be sprayed on to this pack,[1] and, as there is nearly always some mouth breathing before the onset of surgical anaesthesia, the ethyl chloride will be inhaled. This technique overcomes the necessity for any modification to existing equipment and has been in use for many years. In fact, at the B.M.A. Annual Meeting in Belfast in 1938 Dr. Ronald Jarman showed an excellent colour film describing this method, though many of us had been using it for a long time.

REFERENCE

1 Goldman, V., *Aids to Anaesthesia*, 1957, 4th ed., p. 270.

Inoculation Campaigns and Viral Hepatitis.—Brigadier G. T. L. ARCHER (London, S.W.1) writes: There can be no doubt that the ideal method of avoiding the risk of transmitting infection by inoculation is the use of a fresh syringe and needle for each patient until, possibly, as suggested in my earlier letter on a kindred subject (*Journal*, July 21, 1956, p. 177), needleless jet injection or multipuncture replaces the needle and syringe. So far I agree with the answer published under "Any Questions?" (January 4, p. 55) to a query on how to avoid the risk of transmitting viral hepatitis.

It was somewhat surprising, though, to read the alternative there suggested as acceptable. The writer, in speaking of using a fresh needle, might be taken to imply that the used needle may be taken off the syringe, without first being sterilized, and replaced with a fresh sterile one. Further, he speaks of the syringe being changed only when its contents have been finished, thus also implying that several doses may be taken into the syringe at a time and given to a series of persons rather than a syringe being completely emptied and refilled for each of them. The work of Evans and Spooner[1] and that of Fleming and Ogilvie[2] have shown that neither of these implied procedures is safe when using an ordinary syringe, though with specially constructed needles and syringes[3 4] the needle may be so removed and changed. On this account the War Office[5] recommends that only one dose should be taken into a syringe at a time, and that after this is expelled into a patient the needle should be sterilized *in situ* by dipping in hot oil or boiling water while the piston is firmly held against the base of the barrel of the syringe—that is, the method advocated by Fleming and Ogilvie.[2]

There remains the question of the need to withdraw the plunger to ensure that a vein has not been entered accidentally when a subcutaneous or intramuscular injection is intended.[6] I have already commented in the letter referred to above that if this is considered essential there is no really acceptable alternative, when using the conventional syringe and needle, to the use of a freshly sterilized syringe and needle for each patient. I would add that even if circumstances dictate resterilization of the needle only, with either aspiration tests or several doses in the syringe (or both of these procedures), such resterilization is more likely to achieve its aim if carried out *in situ* rather than after removal of the needle from the syringe.

REFERENCES

1 Evans, R. J., and Spooner, E. T. C., *Brit. med. J.*, 1950, **2**, 185.
2 Fleming, A., and Ogilvie, A. C., ibid., 1951, **1**, 543.
3 Gross, W. O., *Dtsch. med. Wschr.*, 1954, **79**, 829.
4 War Office, *Memorandum on Immunological Procedures*, 1956, H.M.S.O., London.
5 Voorhorst, R., *Ned. T. Geneesk.*, 1954, **98**, 1984.
6 Scurr, C. F., *Brit. med. J.*, 1956, **1**, 1289.

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